Twenty-second Annual Meeting — Chicago, Illinois
June 7-10, 1956

VOLUME XXIX NUMBER 5

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

AMERICAN COLLEGE OF CHEST PHYSICIANS

PUBLISHED MONTHLY

MAY
1956

PUBLICATION OFFICE, CHICAGO, ILLINOIS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

Entered as Second Class Matter at the Postoffice at Chicago, Illinois

Fourth International Congress on Diseases of the Chest
Cologne, Germany — August 19-23, 1956

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

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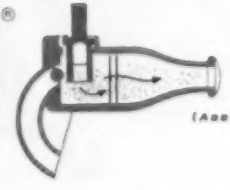

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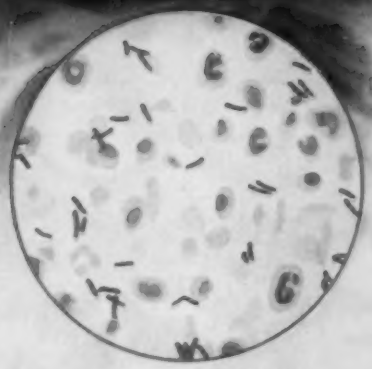

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THIRD ANNUAL SYMPOSIUM ON ANTIBIOTICS
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by
1. Shubin, H., and Heiken, C. A.
2. Morton, R. F.; LaCaille, R. A.; Gold, A., and Prigot, A.
3. Payne, H. M.; McKnight, H. V., and Harden, K. A.

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VOLUME XXIX MAY, 1956 NUMBER 5

CONTENTS

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In a study of four ganglionic blocking agents, Winsor[1] found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson[2] reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.[2,5]

For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."

References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Fraser, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Fraser, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

SUPPLIED: ECOLID Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).

DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

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2	25 mg.	25 mg.
3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

Hospitalized patients		
DAY	A.M.	P.M.
1	50 mg.	—
2	50 mg.	50 mg.
3	100 mg.	50 mg.
4	100 mg.	100 mg.

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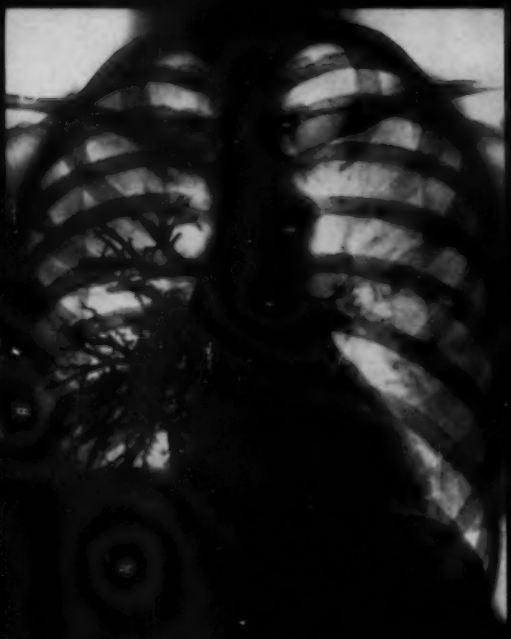
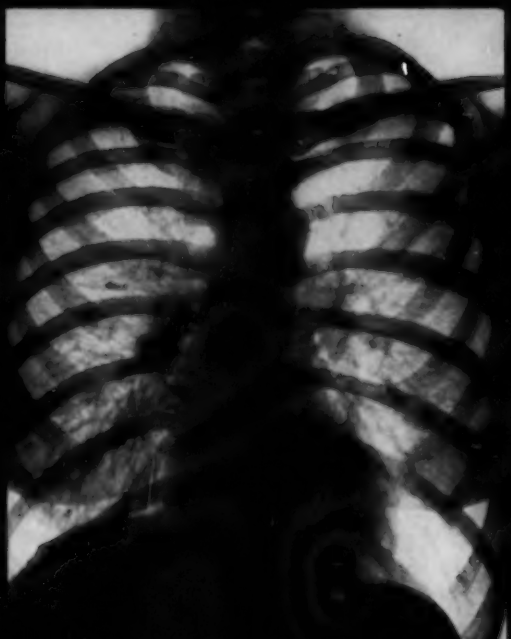


Bronchogram of right lung with VISCIODOL. Note clear outline of bronchi and absence of alveolar filling.



Chest x-ray three days after bronchogram. Note clearing of VISCIODOL and fluid level in right hilar cavity.

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1. Burrascano, J. J.: Sea View Hosp. Bull. *15*:149 (July) 1955.

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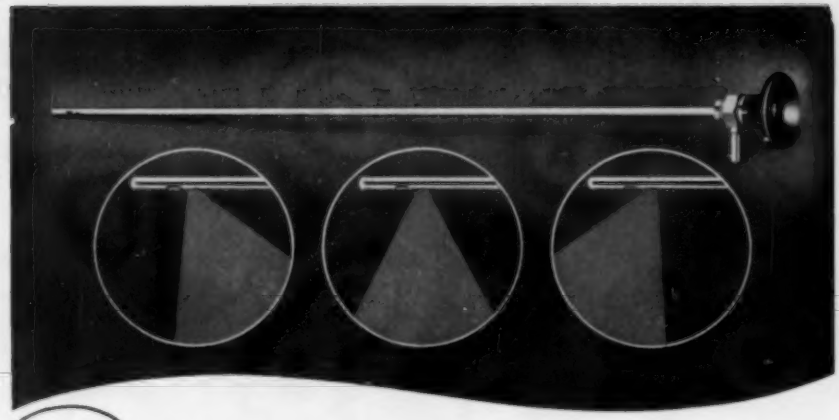

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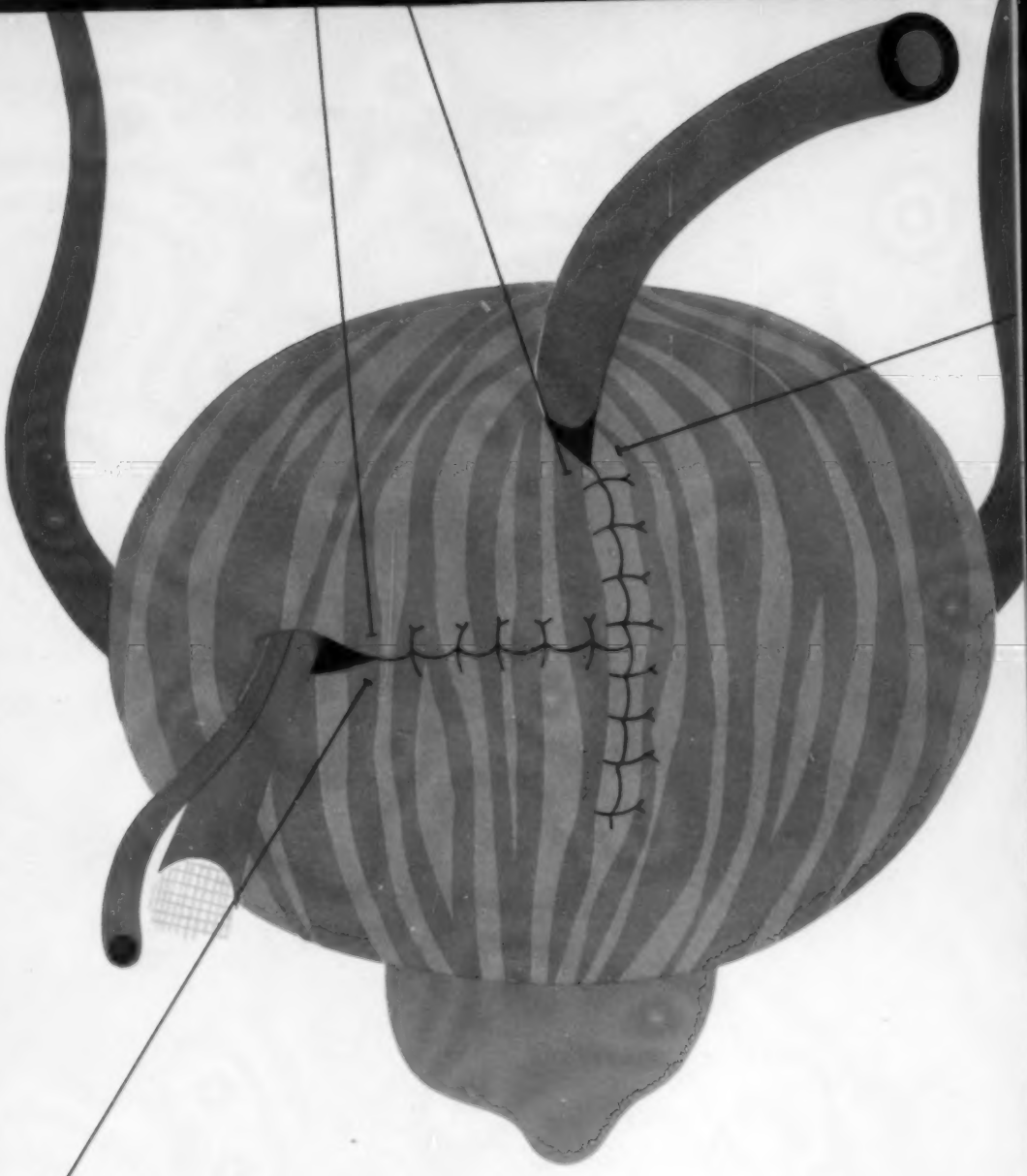

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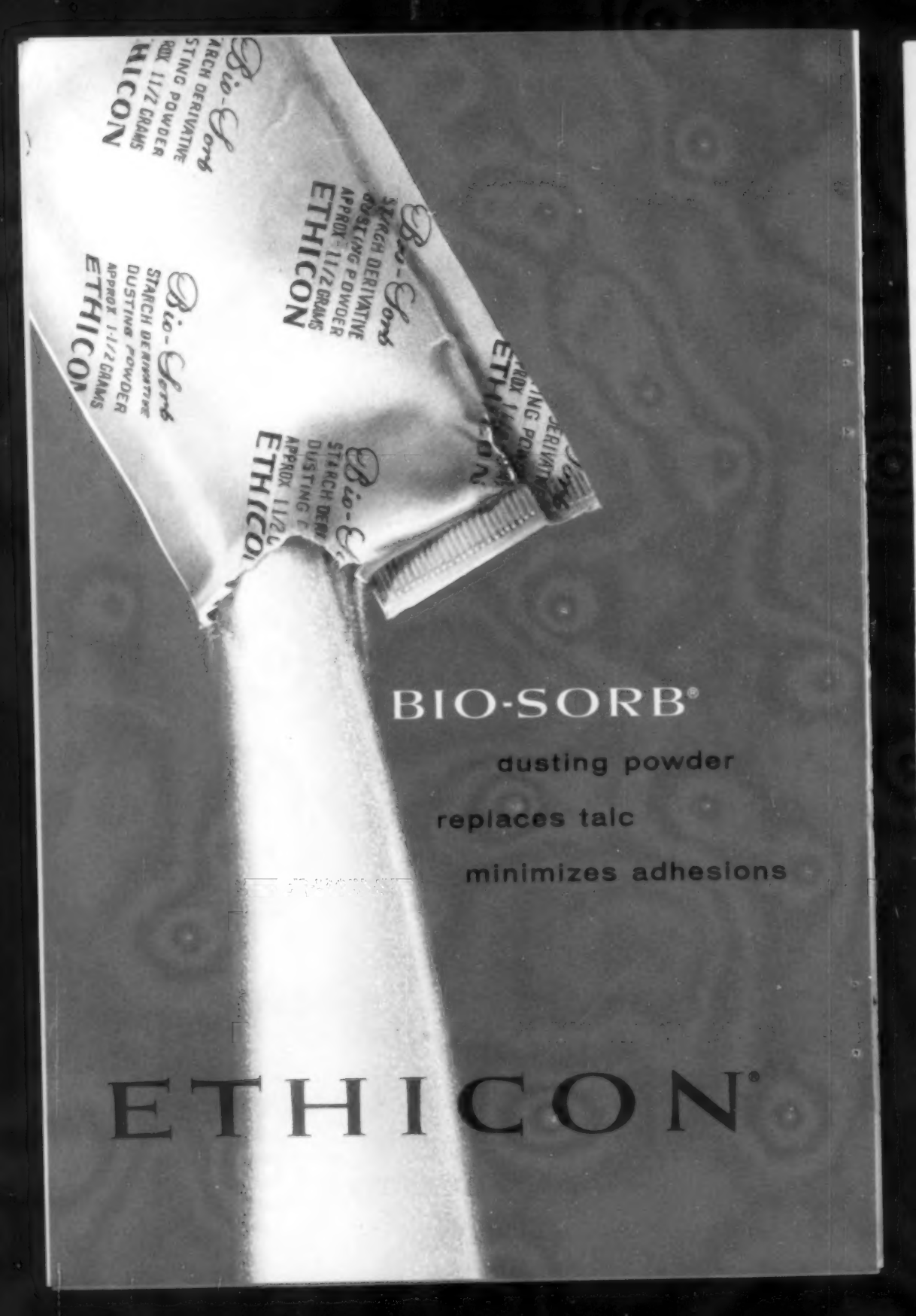
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*T. M.

MC J-65-206

A Laboratory and Clinical Report on Adrenosem® Salicylate

(BRAND OF CARBAZOCHROME SALICYLATE)

History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam[1] in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"[2] enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.[2-7]

(* U.S. Patent 2,581,850)

Sherber, in an early study,[3] concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators[2-7] are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton[8] confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.[7]

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.[4] "We have used 2½ mg.

(½ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.[5] The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagolic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.[6] "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of post-tonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."[5]

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and
nasopharynx surgery;
prostatic and bladder surgery;
uterine bleeding;
postpartum hemorrhage;
dental surgery;
chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

Supplied

Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S.C. Orange, bottles of 50.
Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce bottles.

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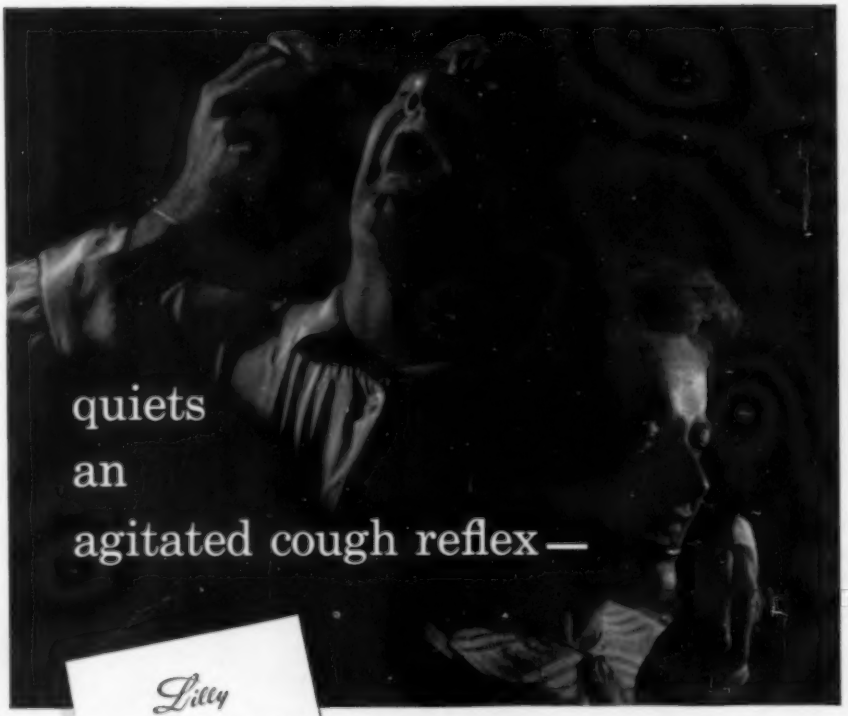

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DISEASES of the CHEST

VOLUME XXIX MAY, 1956 NUMBER 5

Cardiac Septal Defects

1. Ventricular Septal Defect. Analysis of One Hundred Cases Studied During Life

DANIEL F. DOWNING, M.D., F.C.C.P. and HARRY GOLDBERG, M.D., F.C.C.P.

Philadelphia, Pennsylvania

The textbook description of manifestations of ventricular septal defects has resulted in the impression that the lesion is relatively benign. Because we believe this to be an improper assumption we have analyzed 100 patients demonstrated to have the malformation. Inasmuch as atrial septal defects allow the same basic alteration in blood flow—a left to right shunt within the heart—we have conducted a similar study of individuals with this defect.[1]

The individuals in both series met the following criteria: 1) each was studied by one or both of the authors, 2) each was subjected to cardiac catheterization, 3) no patient was chosen or rejected except as he fulfilled the first two requirements; in other words, each series is consecutive. In addition, no patient with a ventricular septal defect was considered if he had another cardiovascular lesion of physiologic significance; the only additional anomaly allowed one with an atrial septal defect was abnormal drainage of pulmonary veins to the right heart, this having only the significance of a larger interatrial communication.

The first section of this report deals with defects of the interventricular septum.

Material

Sex: There were 50 females and 50 males.

Age: Most of the patients were in the pediatric age group, 76 being under 15 years of age (Table I). The youngest was three months; the oldest, 52 years.

Pregnancy Factors: Adequate information concerning the period of gestation is available for 78 individuals. Fifty-one pregnancies (65 per cent) were reported to be entirely uneventful. Eighteen mothers (23 per cent) suffered only nausea and vomiting during the first trimester. Five had one or more episodes of vaginal bleeding during this period. In two there were both nausea and vomiting and vaginal hemorrhage. One with nausea and vomiting had, in addition, a severe upper respiratory infection and another had pneumonia. No pregnancy was complicated by

From the Division of Pediatrics and the Division of Medicine, Hahnemann Medical College and Hospital and the Bailey Thoracic Clinic.

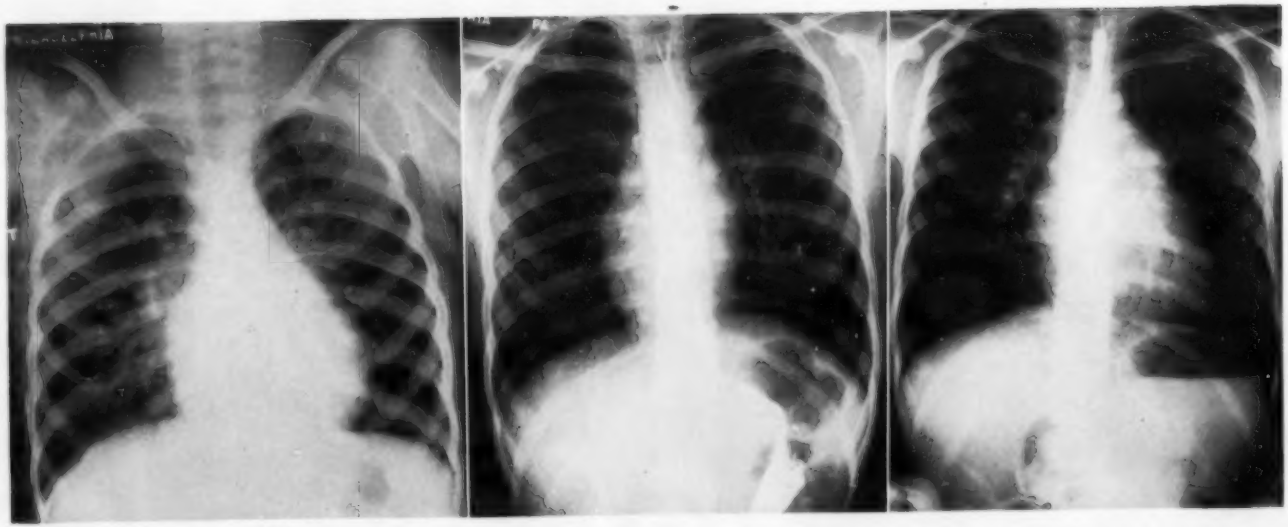

FIGURE 1A FIGURE 1B FIGURE 1C

Figure 1: Variations in postero-anterior roentgenograms in ventricular septal defect. (A) Age 5 years. PA = N.* (B) Age 9. PA = SA.* (C) Age 6. PA = N. For complete information of code see page 481.

TABLE I
AGE DISTRIBUTION OF ONE HUNDRED PATIENTS WITH VENTRICULAR SEPTAL DEFECTS

Birth to 1 year	12
1 to 5 years	27
5 to 10 years	30
10 to 15 years	8
15 to 20 years	7
20 to 30 years	8
30 to 40 years	5
40 years plus	3

rubella or other exanthematous disease. The month of conception and the age of the parents at this time were without significance.

Congenital Defects in Family: For 27 patients specific information in this regard is lacking. Among those remaining there was no instance in which a congenital cardiac lesion was known to be present in a member of the household family. A paternal aunt and uncle of one individual and one cousin of three others were victims of heart anomalies, however. Six additional patients had relatives within the second degree with congenital defects of some nature: tracheo-esophageal fistula (sibling), hare-lip and cleft palate (two cousins), strabismus (father), deafness (aunt) and a central nervous system defect (cousin).

In 76 cases the presence or absence of diabetes mellitus could be determined. One or more members of the immediate family of 24 (31.4 per cent) had the disease.

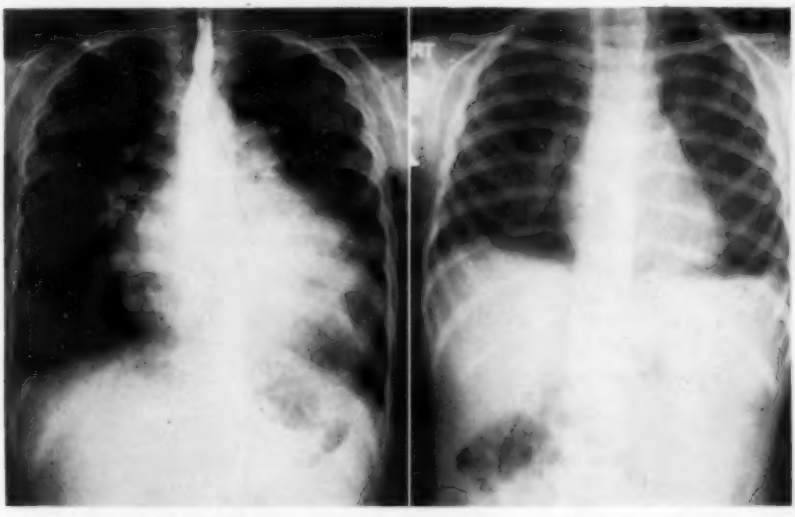

FIGURE 1D FIGURE 1E

Figure 1: Variations in postero-anterior roentgenograms in ventricle septal defect. (D) Age 4. PA = SA. (E) Age 2. PA = N. For complete information of code see page 481.

TABLE II—DEFINITIVE DIAGNOSIS METHODS EMPLOYED IN SERIES

Cardiac catheterization	100
—and angiocardiography	13
—and aortography	6
—and surgery	1
—and autopsy	2
—angiocardiography and surgery	2
—aortography and surgery	1
—surgery and autopsy	3

Methods of Study

All patients were admitted to this hospital and observed for at least two days. Data on each were contributed by history, physical examination, electrocardiogram, roentgenogram and cardiac catheterization. Information was derived from angiocardiography, thoracic aortography, surgical exploration or autopsy in a number (Table II).

Cardiac catheterization was performed under basal conditions, using capacitance electromanometer for pressure determination.* Oxygen determinations were made according to the method of Van Slyke and Neill.[2] As a rule, pressure was recorded continuously as the catheter tip was withdrawn from the pulmonary capillary bed to vena cava, except at the time a blood sample was being obtained. Routinely, at least three samples were secured in the pulmonary circuit (main pulmonary artery and its right and left branches), three from the right ventricle (distal out-flow tract, midchamber, and near tricuspid valve), three in the right atrium (near tricuspid valve, mid-chamber and high) and one from each vena cava. Systemic pressure was measured by cannulation of the brachial or femoral artery and a blood sample drawn from this vessel. Oxygen consumption was measured whenever possible. This could not be accomplished in a number of cases because of difficulties attendant upon age.

Angiocardiography was employed in 15 patients. In 14 the injection of contrast material was made directly into the right atrium via an aortography catheter. In the remaining patient thoracic aortography was intended. A catheter was introduced into the brachial artery and guided to the root of the aorta. It was then manipulated into the left ventricle and by chance the tip passed through a defect into the right ventricle. Here the contrast substance was injected.

Thoracic aortography was performed on seven occasions. The injection of radiopaque material was made directly into the ascending aorta via a catheter inserted into the brachial artery.[3]

Results

History: Eighty-nine patients had symptoms which could have been cardiac in origin. The remaining 11 were children in whom parents had noted nothing abnormal. Eight were below three years of age.

Fatigue was the most commonly occurring symptom, being present in 72. All grades of severity were reported, from consciousness of tiring

*Sanborn Company.

before one's fellows to inability to perform muscular work for longer than a few minutes.

Shortness-of-breath on exertion was of equal importance, 71 having this complaint. It, too, varied in degree, from onset of "puffing" earlier than one's playmates to dyspnea, orthopnea or paroxysmal nocturnal dyspnea.

In 39 cyanosis had been noted at some time. Undoubted manifestations of cardiac failure had been present in 22. Chest pain localized to the cardiac area had been felt on more than three occasions by 13. Chronic cough was mentioned by 12. Paroxysms of rapid heart action (known in six to have been paroxysmal atrial tachycardia) had been present in eight. Hemoptysis had occurred in six, syncope in six. Eight had had one symptom; 11, 2; 28, 3; 22, 4; 12, 5; and 4, 6. It should be mentioned that 52 individuals were noted to perspire profusely.

Weight gain during infancy had been poor in 31 and motor development was delayed in an equal number.

Five females had had one or more pregnancies (total, eight) without difficulty. Menses were irregular in two of the adult females.

Thirty-three had had pneumonia or other severe respiratory infection at least once. Because there seems to be an impression that respiratory infections are particularly common in cardiac conditions allowing increased pulmonary flow, 100 cases of proved pulmonary stenosis were analyzed in regard to this factor. Twenty-six were found to have had pneumonia on one or more occasions. The difference in numbers cannot be regarded as significant.

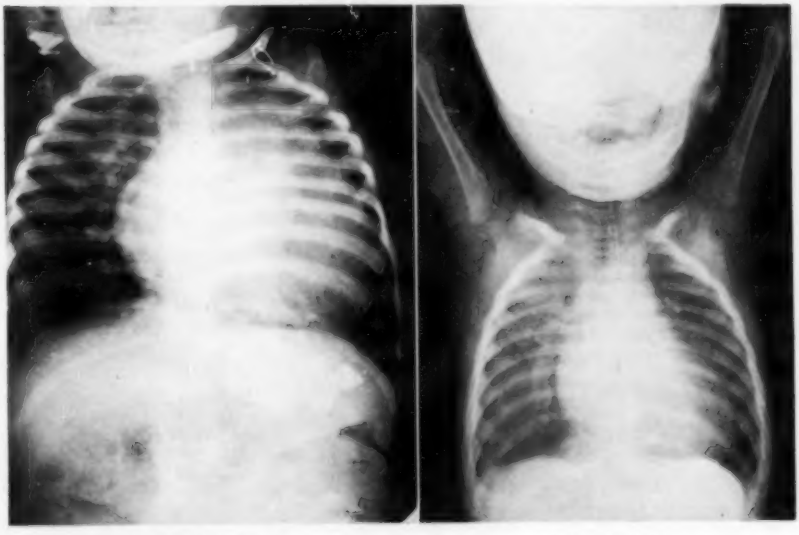

FIGURE 1F FIGURE 1G

Figure 1: Variations in postero-anterior roentgenograms in ventricular septal defect. (F) Age 1. PA × SA.* (G) Age 4 mos. PA = SA. For complete information of code see page 481.

Two in the series had had cerebral vascular accidents, one an infant of 13 months, the other an adult of 41 years.

Known subacute bacterial endocarditis had not occurred in any member of the group, nor had any a history of prolonged febrile illness of unknown cause.

The Physical Examination: The most frequently encountered physical sign was cardiac murmur. It was systolic alone in 81. In one there was only a diastolic murmur. One individual had none. In 17 there were both systolic and diastolic murmurs. The greatest intensity of the systolic murmur was at the left sternal border in 91 cases: in the second and third interspaces in seven, the third in 25, the fourth in 24, the third and fourth in 27, the fourth and fifth in 5, the fifth in 1, the fourth, fifth and sixth in 1, the second to the fifth in one. One patient's murmur was loudest at the apex. In another it was best heard in the right third and fourth interspaces. Our notes regarding location in five individuals are not satisfactory. We noted transmission in 89 cases. There was none in seven, along the left sternal border in seven, to the axilla in two, over the anterior thorax in 24, the left anterior and posterior thorax in 47, the left and right anterior and the left posterior thorax two. An early diastolic murmur was located in the second left interspace in one; the third in two; the fourth in three; the fourth and fifth in two; the third, fourth and fifth in one. A mid-diastolic murmur was heard at the apex in eight. In the patient in whom only an early diastolic murmur could be heard it was localized at the third and fourth left interspaces.

A systolic thrill, located at the interspaces where the murmur was best heard, was present in 65. In no patient was there a diastolic thrill.

The second sound at the base to the left of the sternum was definitely accentuated in 68 patients. The sound was inaudible in six and considered to be normal in the rest. The mitral first sound was accentuated in three.

In 52 there was thoracic asymmetry, the left anterior chest being more prominent than the right.

Evidence of cardiac enlargement, either to percussion or by the point of maximum impulse, was present in 46.

Cyanosis was visible in 29, varying from slight discoloration of the lips and nailbeds to a deep blue in these areas and generalized duskiness.

Clubbing of the digits was present in 14, but was not marked in any individual.

A prominent venous pattern over the anterior thorax was seen in two, systolic nodding of the head in two, hemiplegia in two, erythema of the distal portions of the digits in one.

Associated congenital anomalies were apparent in 21. A wide variety of conditions was present, including mongolism in three, tuberous sclerosis in one and widespread ectodermal dysplasia in one.

Roentgenological Examination: All patients were fluoroscoped by one or both authors. Because the fluoroscopic findings could not be verified at the time the cases were reviewed, they are not considered in detail. It

may be stated that there was close agreement with film observations, although structures appeared to be somewhat larger on the screen. In approximately 45 per cent a note was made to the effect that pulsations of the main pulmonary artery and its right and left branches were considered to be increased.

All films (postero-anterior, right and left obliques and left lateral with barium or lipiodol swallow) were interpreted. Only 98 patients can be considered. The films of one could not be found; another has such marked kypho-scoliosis that no decision was possible as to the heart shape, chamber or great vessel size. Notes were made in each case in regard to several factors.

Pulmonary vascular markings. Attention was focused on the vessels in the lateral two-thirds of the lungs. In the series one had decreased markings and 10 were considered to exhibit normal size of vessels. The remainder showed increased prominence of their peripheral vasculature: 23 were graded one plus; 31, two plus; 30, three plus and 3, four plus.

Main pulmonary artery. The size of this structure was determined in the postero-anterior and the right anterior oblique views. Considering both projections, nothing could be said in two cases because of severe scoliosis. Twenty-four were believed to be normal. Of those remaining there was one plus enlargement in 16, two plus in 29, three plus in 24, four plus in 3.

Heart size. This was normal in 17. In 29 it was enlarged one plus; in

*PA = N: PA pressure normal. PA = SA: Pulmonic and systemic pressure equal. PA × SA: Pulmonary hypertension, but level significantly lower than systemic.

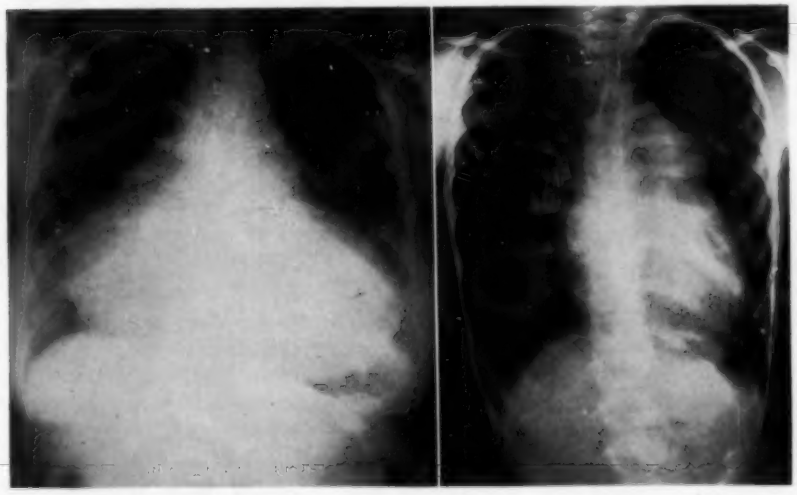

FIGURE 1H FIGURE 1I

Figure 1: Variations in postero-anterior roentgenograms in ventricular septal defect. (H) Age 20. PA = SA. (I) Age 9. PA = SA. For complete information on code see above.

21, two plus; in 23, three plus; in 4, four plus; in 1, five plus; in 1, six plus. Representative films are reproduced in Fig. 1.

Left border and apex. The left border was rounded in 30. In 40 it was rounded, with elevation of the apex. In 3 it was snouted, with elevation of the apex, while in 3 it was pointed. In 10 there was a long left border with depressed apex. The remaining patients showed no abnormality.

Right ventricle. In the right anterior oblique view this chamber was normal in 24. One plus encroachment on the retrosternal space was present in 23, two plus in 17, three plus in 19, four plus in 8, five plus in 1. Six films were unsatisfactory.

The Electrocardiogram: Ninety-one tracings were analyzed. Those of four patients could not be found and although the interpretations were in the records they were excluded. Five included no precordial leads and they, too, were excluded.

Right ventricular hypertrophy pattern was definite or strongly suggested in 54 tracings (59 per cent). Left ventricular hypertrophy was suggested in one. Another individual with definite right heart strain showed, also, suggestive evidence of left ventricular hypertrophy. First degree atrio-ventricular block was present in three; delayed intraventricular conduction in five; right bundle branch block and first degree atrio-ventricular block in one, focal right bundle branch in one, incomplete right bundle branch block in one, Wolfe-Parkinson-White phenomenon in one.

Cardiac Catheterization: Ninety patients showed a rise in oxygen content of one volume per cent or more from right atrium to right ventricle. Causes of such a rise other than a ventricular septal defect were excluded if any suspicion of their presence existed.

Of those failing to show such a rise, two were believed to have an atrial septal defect because of a significant increase in oxygen content from venae cavae to right atrium, with no further increase at the ventricular level. Both were surgically explored and both died. At autopsy only a defect in the membranous portion of the interventricular septum was found. In two catheterization data were incomplete because of failure to secure proper blood samples, either in atrium or ventricle. One later died and post-mortem examination revealed as the sole lesion a defect in the membranous ventricular septum. The other was considered to have a ventricular septal defect and was operated upon in the hope of closing it by means of a tube graft of pericardium. It was found to be too large. In one individual the catheter passed from right ventricle to the left. It was obvious from the position of the catheter in all views and from the continuous pressure tracing that it had not arrived in the left ventricle via an interatrial septal communication and the mitral valve. This is the only one in the series believed to have a defect of the muscular portion of the septum. In the remaining five there was found to be the same pressure in the right ventricle, pulmonary artery, and aorta or systemic artery. A right to left shunt was present in all as determined by arterial oxygen saturation, calculation of flows, and the presence of obvious cyanosis. In

three, angiocardiography demonstrated simultaneous opacification of right ventricle, aorta and pulmonary artery.

For 16 patients arterial oxygen saturation data are not available. Of the others, a right to left shunt was indicated in 34, saturation being below 90 per cent, the figure regarded as borderline for infants and children under sedation in this laboratory. Thirty-two of these demonstrated a significant step-up in oxygen content from right atrium to ventricle.

Shunts were calculable in 44 patients by virtue of having determined oxygen consumption at the time of catheterization. They ranged between an overall shunt from left to right of 11.8 liters/minute to one of 4.4 liters per minute from right to left. In a number of these cases, total pulmonary resistance and right ventricular work were calculated. The former varied from 66 to 4800 dynes sec./cm.^{5}; the latter from 0.15 to 15.35 Kgm./minute.

The catheter tip passed from the right ventricle to the aorta in 11 patients. In only one of these did it also pass into an area definitely determined to be the body of the left ventricle. Six gave evidence of a shunt in both directions; five showed only left to right flow. In three additional individuals the tip passed from the right ventricle to the apical portion of the left ventricle. Two had left to right shunts; the other, mentioned previously, had no shunt. In six the catheter tip passed from right atrium to left. Passage was via a patent foramen ovale in each instance because, 1) there was no evidence of a shunt in either direction at the atrial level, 2) in all instances the left atrial pressure was higher than that in the right chamber, and 3) the traverse of the septum was made only once.

Seventy-two in the group had right ventricular and pulmonary artery hypertension. (Systolic pressure 30 mm. or higher.) In 48 the pulmonic

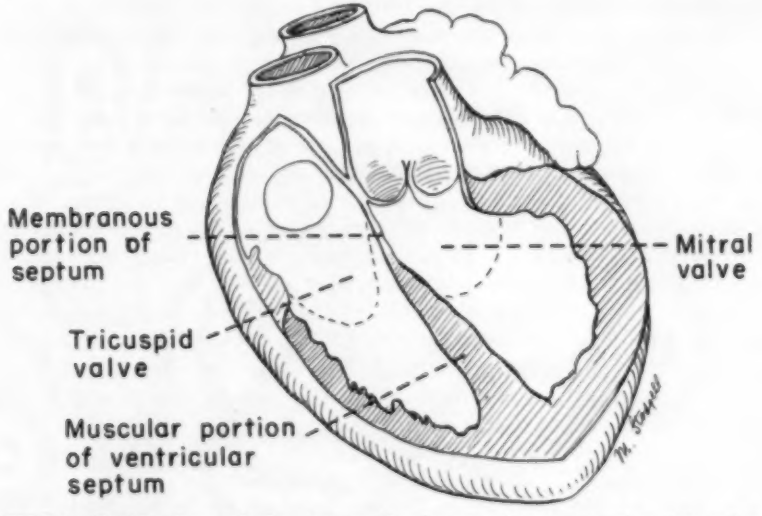

FIGURE 2: Sketch of ventricular septum showing membranous portion (a) and muscular portion (b).

pressure was of the same order of magnitude as systemic (determined by direct catheterization of the aorta or cannulation of a systemic artery). The remaining 24, while having pulmonary systolic pressure above 30 mm. Hg., showed a spread of difference between pulmonic and systemic pressures from 28 to 80 mm. of mercury.

Pulmonary venous capillary pressure was normal in all cases. Systemic blood pressure was also within normal range.

Comment

These data indicate that the classic view of ventricular septal defects is erroneous. It is *not* a lesion which is of only academic interest, which produces few or no symptoms, which causes no roentgen or electrocardiographic abnormalities, which is compatible with a normal life.

The average patient has one or more symptoms which may be attributed to his condition. Fatigue and shortness of breath are the most common. Cough and syncope occur. Cyanosis at some time appears in many. Cardiac failure may be expected in approximately 20 per cent. The majority of individuals show, on x-ray film examination, increased prominence of peripheral pulmonary vascular markings, dilatation of the main pulmonary artery, cardiac enlargement to the left with rounding of the left border, and prominence of the right ventricle in the right anterior oblique view. The electrocardiogram shows definite or suggestive evidence of right ventricular hypertrophy in approximately one-half. Conduction defects are seen occasionally.

In this series the character of the murmur and its location have varied greatly. It has been faint or very loud, harsh and low pitched, blowing and high pitched, has appeared to originate superficially or deep within the thorax, has been heard best at all points along the left sternal border, has been transmitted widely or narrowly.

The systolic murmur is probably due to blood flow through the defect. Its character depends upon many factors: size and exact location of the defect, magnitude of flow, degree of pulmonary resistance. It does not appear to be true that "the smaller the defect, the louder the murmur." There was no constant correlation in our group between size (as measured by shunt and relative pressure in both systems) and intensity. The location of the murmur depends upon the degree of rotation of the heart as a result of right ventricular hypertrophy and upon the area of septum involved.

Of the 18 patients with diastolic murmurs, 16 had pulmonary hypertension. In those in whom the murmur was heard along the left sternal border it was probably due to pulmonary insufficiency. The right ventricle expels its blood. As the quantum meets the resistance at the small vessel level its forward progress is hindered. To accept the last portion forcibly ejected by the ventricle the main pulmonary artery dilates and the pulmonary ring is stretched. This renders the pulmonary valve incompetent and, the ventricle now being in diastole, a small amount of blood falls back into the unguarded chamber, producing a murmur.

A second systolic murmur in the presence of an uncomplicated interventricular septal defect may be explained in a number of ways. 1) It may

be functional. The presence of an organic lesion does not militate against the production of the same type of murmur heard in normal individuals. 2) It may be due to relative pulmonary "stenosis." Given a dilated pulmonary artery and a pulmonary ring of normal size, eddy currents may be set up as the blood rushes through the valve, thus producing a murmur. 3) It may be due to relative tricuspid insufficiency. In the presence of marked pulmonary resistance and right ventricular hypertension there may be stretching of the tricuspid ring so that during ventricular systole a small amount of blood escapes into the right atrium.

The electrocardiogram is not characteristic. Although it has often been represented as being normal in this condition, one would logically assume that an interventricular septal defect of significant size would manifest itself by evidence of extra right ventricular work. This is borne out in this study. In some patients the additional work imposed by the shunted blood, even with normal pulmonary resistance, results in hypertrophy of the muscle cells which is reflected in the electrocardiogram. In others, it probably is the increased resistance which necessitates hypertrophy. The few individuals who in spite of pulmonary hypertension have a normal tracing are probably blessed with an extraordinary myocardium which can, without demonstrable change, meet the extraordinary demands made upon it. We have seen references in the literature to the effect that evidence of left ventricular hypertrophy is to be expected in interventricular septal defect. This seems unreasonable to us and in the present series it was suggested in only one patient.

Roentgenologic findings are not characteristic. The increased pulmonary flow results in increased prominence of the peripheral pulmonary vessels, dilatation of the main pulmonary artery and, in some patients, of its right and left main branches. Right ventricular hypertrophy results from the increased work. Because this chamber is anterior and inferior, thickening of its wall tends to move the apex upward and to produce rounding of the left border. Great degrees of hypertrophy, with or without dilatation, produces increased prominence of the heart shadow anteriorly when viewed in the right anterior oblique position.

In reviewing the roentgen data in a comparable series of atrial septal defects, the chief difference has been that the patients with atrial septal defects tend to have larger right and left branches of the main pulmonary artery. However, individuals with either defect may present the same roentgen features, throwing differentiation by the roentgenologist into the field of the guess.

Satisfactory premortem diagnosis of an interventricular septal defect depends upon laboratory study. Cardiac catheterization, alone or in combination with contrast roentgen procedures, is necessary. In the majority, catheterization is sufficient. If the average oxygen content of three samples of blood from various areas in the right ventricle is 1 volume per cent or more greater than that of three right atrial samples, a left to right shunt at the ventricular level is present. If the catheter passes from the right ventricle into the pulmonary artery and also into the aorta and if sys-

tolic pressure in the three areas is of the same order of magnitude a ventricular septal defect is present even though there is no evidence of a shunt. If the catheter does not traverse the defect in a patient whose pulmonary artery, right ventricle and peripheral artery systolic pressure is the same, and who has no evidence of a shunt, contrast study is indicated. In such cases, angiocardiography, particularly if the contrast substance is injected into the right heart via a catheter, will often demonstrate simultaneous opacification of right ventricle, pulmonary artery and aorta.

In some individuals with ventricular septal defect, a rise in oxygen content is not determined in the right ventricle but the pulmonary artery samples show a significant increase. In these cases, if the electrocardiogram shows right ventricular hypertrophy and if pulmonic pressure is significantly lower than systemic, the patient has a ventricular septal defect. If, in the same circumstance of increased pulmonary artery oxygen content, pulmonic and systemic pressure is equal and the electrocardiogram shows right ventricular hypertrophy, the patient may have a ventricular septal defect, an aortic septal defect or a patent ductus arteriosus. The differentiation requires employment of thoracic aortography.

Catheterization is misleading in some instances. In four of our patients, only two of whom are included in this series, the left to right shunt appeared to be at the atrial level, there being a rise in oxygen content of more than two volumes per cent from venae cavae to right atrium without further rise in the ventricle. In all, pulmonary and systemic systolic pressures were identical. The true location of the defect was demonstrated at autopsy or operation in each case. Obviously, in these cases there was incompetence of the tricuspid valve, allowing a shunt from the left ventricle directly into the right atrium.

Discussion

The physiologic effect of a defect of the interventricular septum depends upon its location and its size. The septum is constituted of two distinct portions, an extensive muscular and a smaller membranous (Fig. 2). Aberration in development of either may result in a defect.

The muscular septum is affected much less frequently than the membranous. We have only very rarely seen at autopsy a localized defect of the muscular portion unaccompanied by a severe malformation of some other part of the heart. In the living patient we have been satisfied on only one occasion that such a defect has been demonstrated, unaccompanied by other cardiac anomaly. This type of defect is probably of no physiologic significance, due to the fact that the septum is engaged in the contracting action of the ventricles. The tendency, therefore, will be toward diminution in the size of the communication during systole, its margin contracting. Left to right flow, then, is less than potential, even though in this part of the cardiac cycle left ventricular pressure is higher than right. During diastole the pressure in both pumping chambers is similar and although the defect is now of maximum size there is little or no blood flow through it.

Absence of all or a portion of the membranous septum is common. All individuals in this series who were autopsied or surgically explored proved to have such defects. The membranous septum is not dynamic. An aperture in it remains the same size throughout the cardiac cycle. Flow through the hole, both in magnitude and direction, depends upon its size and upon resistance to the movement of the mass of blood in the ventricles. The resistance becomes the more important criterion.

Normally, the resistance to right ventricular outflow is relatively low, being only 15 to 25 per cent that of the left ventricle. Inasmuch as intraluminal pressure is dependent upon resistance, left ventricular ejection force is normally greater than right. Therefore, a static communication between the two systems will favor a left to right shunt. If the communication be small, relatively little blood may be shunted because the remaining septum offers greater resistance than does the peripheral arterial circuit. A larger defect, on the other hand, means less septum resistance. Left ventricular blood, meeting relatively high systemic resistance, will in proportionately greater amount traverse the defect into the right ventricle.

A phenomenon which in most respects may be considered peculiar to lesions allowing left to right shunts alters this basic process. In such malformations—ventricular, atrial and aortic septal defects, patent ductus arteriosus, anomalous pulmonary vein drainage—there is a tendency to the development of increased pulmonary resistance.

The regulation of resistance to blood flow in the pulmonary circuit and, hence, the determinants of pressure in that system are not completely understood and appear to differ, qualitatively and quantitatively, from those in the systemic circuit. Just as systemic hypertension may exist with normal pulmonary pressure, pulmonary hypertension with normal systemic pressure is found in a variety of conditions. It may be primary, i.e., no explanatory pathologic changes are found, or early there may be only widely scattered vascular changes which in their total could not explain the high pressure.[4] It may be due to periarteritis nodosa confined to the pulmonary vascular bed, although in our experience, other changes have been present in addition.[5] It may be due to parenchymal disease. It may be due to heart failure or to acquired or congenital obstructive lesions of the left heart. It may, as mentioned above, be found in congenital cardiac lesions allowing left to right shunts.

In all these conditions, except acute left ventricular failure, we assume that the cause of the hypertension must, in major part, be increased resistance to pulmonary flow. In the individual with no demonstrable anatomic changes or only scattered changes in the small vessels the increased resistance is probab'y due to diminution in size of the lumina of the components of the vascular bed by contraction, resulting from, one may speculate, a neuro-chemical mechanism. In those cases exhibiting periarteritis nodosa, even if there is no underlying vascular change, there is objectively determinable reason for the resistance, the process causing narrowing of lumina by changes in or about the vessel walls. Parenchymal disease impedes pulmonary flow by external pressure on the small vessels. Obstruc-

tive lesions of the left heart prevent ready flow of blood from the pulmonary system, and vascular changes take place therein which result in increased resistance.

The causes of pulmonary hypertension in congenital cardiac defects allowing a left to right shunt are probably many. The increased flow, itself, appears to be effective in raising pressure to some degree. We have seen a drop in pulmonary artery pressure a short time after obliterating the communication between the two systems in patent ductus arteriosus and atrial septal defect.[6] The pressor effect in these cases may, of course, have been due to neuro-chemical forces, with contraction of vessels being released upon removal of the stimulus.

Anatomic narrowing of the lumina of pulmonary vessels is a more easily demonstrable cause of hypertension. The vascular changes consist of intimal and medial thickening. The cause is unknown. We presently favor a hypothesis which views a sequence of functional and anatomic changes. As a result of an increase in pulmonary flow of a certain magnitude,* the small vessels contract as a means of limiting the flow. The paucity of muscle elements in the wall of the vessels does not allow sustained contraction without change and there begins the process of medial hypertrophy. At the same time, the hypertension which has resulted from the contraction causes changes to appear in the intima, an effect of direct trauma. Thus, a progressive cycle is instituted.

We conclude that in the majority of patients with ventricular septal defects who have increased pulmonary pressure this has developed over a period of time. Unfortunately, our data merely suggest and do not prove the hypothesis. The variations in pressure, from borderline normal to systemic, we feel are significant. In only one case do we have concrete evidence. This child was catheterized at 21 months of age. Right ventricular and pulmonary artery systolic pressure was 11 mm. of mercury. She was recatheterized at four and one-half years and the pressure was now 40 mm. of mercury. Obviously, in the 33 months interval something occurred to increase pulmonary resistance. This was, probably, a narrowing of the pulmonary vessels. We believe that were serial catheterizations performed on all patients with ventricular septal defects, in a large number this same picture would unfold: as a result of a left to right shunt of a certain magnitude, consequent upon a defect of a certain size, progressive changes in the pulmonary vascular bed take place which result in increasing resistance to flow. The greater the flow, the greater the likelihood of hypertension developing early.

With increasing pulmonary resistance, pressure in the right ventricle gradually rises. (That a static defect between the two systems does not necessarily result in the same pressure in both ventricles is obvious from the variations in this series.) As right heart pressure rises the magnitude of the left to right shunt must decrease. The resistance is progressively greater and eventually a state of balance is reached in which, resistance in both circuits being equal under basal conditions, there is no appreciable

*The increased oxygen content may well play a role.

flow through the defect. With activity and increased demand there may be a slight shunt in either direction. Naturally, at degrees of resistance less than this, even a right to left shunt may occur under stress, accounting for episodes of cyanosis in patients with a relatively wide difference in pulmonary and systemic pressures. Ultimately, resistance to pulmonary flow becomes greater than that to systemic flow and a constant right to left shunt, with the appearance of chronic cyanosis, develops. Pulmonary artery pressure does not then mirror resistance because the septal defect acts as an escape vent. Diversion of blood from its proper channel may be less than would be expected because of the natural lines of force exerted upon the mass of blood in the right ventricle.

Thus, there develop the clinical features of the "Eisenmenger complex." In one patient the necessary conditions may exist very early in infancy; in another not until relatively late in life. In the one, the characteristics of fetal pulmonary vasculature may persist;[7] in the other they may disappear, only to reappear, in effect if not in kind, with advanced age. We feel strongly that there is no anatomic entity demanding this eponym. We have never observed at autopsy a heart which has satisfied the criteria: high ventricular septal defect plus over-riding of the aorta. In those so described by the pathologist one may, it is true, look into the aorta from either ventricle; this is possible, too, in the condition they describe merely as a defect of the membranous portion of the ventricular septum. In a number of specimens said to exhibit over-riding of the aorta we have demonstrated that actually the remnant of the interventricular septum is in direct line with the medial wall of the aorta and, anatomically, the vessel derives its "origin" in entirety from the left ventricle. Functionally, alone, there is biventricular origin of aortic flow. Parenthetically, it might be stated that in the so-called tetralogy of Fallot we probably should expect anatomic over-riding of the aorta only in those patients with a right aortic arch.

SUMMARY AND CONCLUSIONS

Certain data collected in the course of study of 100 consecutive patients with ventricular septal defect in whom right heart catheterization was performed have been presented.

Although the malformation has been thought to be of little significance our observations indicate that it is of serious import. The majority of victims have symptoms. Cardiac failure occurs relatively early in life in a large number. Roentgen and electrocardiographic abnormalities are the rule.

Pulmonary hypertension is present in a large number of patients. We believe that the large pulmonary flow results in functional contraction of the small pulmonary vessels. This results in increased resistance to flow and increased pulmonary pressure. Anatomic changes develop to further increase resistance. The direction of flow through the defect thus may change and a constant right to left shunt ensue. This is the natural history of those patients who are classified as having the Eisenmenger complex, a term which should be abandoned.

The symptoms and physical, roentgen and electrocardiographic signs of the defect are not characteristic. Diagnosis depends upon cardiac catheterization, supplemented in certain cases by contrast roentgen studies.

RESUMEN Y CONCLUSIONES

Se presentan algunos datos recogidos en el curso del estudio de 100 pacientes consecutivos con malformación septal ventricular y en los cuales se cateterizó el corazón derecho.

A pesar de que se ha pensado que la malformación citada carece de importancia, nuestras observaciones muestran que es de gravedad. La mayoría de las víctimas presentan sintomatología. La insuficiencia cardiaca se presenta en un gran número a una edad relativamente temprana. Por lo regular hay anormalidades roentgenológicas y electrocardiográficas.

La hipertensión pulmonar se presenta en un gran número de pacientes. Creemos que el aumento del flujo pulmonar trae como consecuencia una contracción funcional de los pequeños vasos pulmonares. Esto tiene como resultado una resistencia aumentada al flujo y un aumento de la presión pulmonar. Los cambios anatómicos tienen lugar con un aumento subsecuente de la resistencia. La dirección de la corriente a través de la malformación puede por lo tanto modificarse y se establec un corto circuito de derecha a izquierda constante. Esta es la historia común de los pacientes clasificados como con complejo de Eisenmenger, término que debería abandonarse.

Los síntomas y los signos físicos, roentgenológicos y electrocardiográficos de la malformación no son característicos. El diagnóstico se basa en la cateterización cardiaca, suplementada en ciertos casos con estudios radiográficos con contraste.

RESUME

Les auteurs rapportent certaines constatations faites au cours d'une étude portant sur 100 malades vus consécutivement, atteints de malformation de la cloison ventriculaire et chez lesquels le cathétérisme du coeur droit fut pratiqué.

Bien qu'ils avaient eu l'impression que la malformation était de peu d'importance, leurs observations montrent qu'il y avait lieu de la prendre en grande considération. La majorité des malades présentaient des symptômes. L'insuffisance cardiaque apparut relativement tôt chez un grand nombre d'entre eux. Les anomalies radiologiques et électrocardiographiques furent la règle.

L'hypertension pulmonaire existait chez un grand nombre de malades. Les auteurs estiment que le débit pulmonaire élevé résulte de la contraction fonctionnelle des petits vaisseaux pulmonaires. Ceci résulte de la résistance accrue au débit et l'augmentation de la pression pulmonaire. Des modifications anatomiques provoquent un accroissement ultérieur de la résistance. La direction du débit à travers la malformation peut alors se modifier et il peut en résulter un shunt constant de droite à gauche. C'est l'histoire normale de ces malades qui sont classés comme ayant le complexe d'Eisenmenger, terme que l'on devrait abandonner.

Les symptômes et les signes physiques, radiologiques et électrocardiographiques de la déformation ne sont pas caractéristiques. Le diagnostic dépend du cathétérisme cardiaque complété dans certains cas par des études radiologiques avec substances de contraste.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Es wird über 100 Patienten mit Ventrikel-Septum-Defekt, bei denen eine Katheterisierung des rechten Herzens durchgeführt wurde, berichtet.

Obwohl man diese Missbildung zunächst nicht für so wesentlich hielt, zeigen unsere Beobachtungen, dass sie von grosser Bedeutung ist. Die Mehrzahl der Kranken weist Symptome auf. Herzerkrankungen finden sich bei jungen Menschen besonders häufig. In der Regel sind röntgenologische und elektrokardiographische Veränderungen nachweisbar.

Bei einer grossen Zahl von Patienten findet sich pulmonaler Hochdruck. Wir glauben, dass im Lungenkreislauf eine funktionelle Kontraktion der kleinen Gefässe vorliegt. Dieses ergibt sich aus dem wachsenden Widerstand und dem Druckanstieg im kleinen Kreislauf. Ausserdem kommt es durch anatomische Veränderungen zu einem weiteren Anstieg des Widerstandes. Auf diese Weise kann sich durch den Defekt ein dauernder Rechts-Links-Shunt entwickeln. Das ist der übliche Verlauf bei Patienten, die in die Gruppe des Eisenmengerschen Syndroms eingeteilt werden: eine Bezeichnung, die man nicht mehr verwenden sollte.

Symptome, klinische, röntgenologische und elektrokardiographische Befunde sind uncharakteristisch. Die Diagnose hängt von dem Herzkatheterismus ab und wird in gewissen Fällen durch die Röntgen-Kontrastdarstellung ergänzt.

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Acknowledgement: We wish to express our gratitude to Mr. George Raber, Miss Betty Underwood, Miss Ruth Freeman, and Miss Evelyn DeSimone of the Brith Sholom Laboratory Staff for their interest and technical assistance in this study.

Cardiac Septal Defects

II. Atrial Septal Defect. Analysis of One Hundred Cases Studied During Life.

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A previous paper considered certain data derived from a study of 100 patients with ventricular septal defect as the sole lesion.[1] The present communication deals in a similar manner with 100 patients with atrial septal defect. In none was there evidence of an accompanying congenital lesion of the heart valves, the interventricular septum or the great arterial vessels; however, a number had partial anomalous drainage of pulmonary veins. A comparison of the data from the two series is given in Table I.

Material

Sex: There were 72 females and 28 males, a ratio of slightly more than 2.5 to 1.

Age: The age range was two weeks to 61 years. The majority were over 15 years, only 28 being in the pediatric age group (Table II).

Pregnancy Factors: Because of the large number of adults in the series adequate information concerning pregnancy was necessarily limited, their parents usually not being available for questioning. Of the 30 for whom we have relatively reliable data, the period of gestation was uncomplicated in 15. In 11 the first trimester was marked by nausea and vomiting; in two by vaginal hemorrhage; in one by very poor nutrition and in one by nausea and vomiting, vaginal bleeding and occasional syncope. In no case was there a known infection. The month of conception and the age of the parents at that time were without significance.

Congenital Defects in Family: Congenital heart defects were present in the mother of one patient, a sibling of two and in two cousins of another. Other defects included dwarfism in a mother, pyloric stenosis in a son, absence of an ear in a cousin and a hare-lip in an aunt.

Diabetes was present in members of the immediate families of 14 of 70 patients (20 per cent).

Methods of Study

All patients were admitted to this hospital and observed for at least two days. Data on each were contributed by history, physical examination, electrocardiogram, roentgenogram and cardiac catheterization. Angiocardiography, surgery or autopsy gave additional information in a number (Table III).

Cardiac catheterization was performed under basal conditions using

From the Divisions of Pediatrics and Medicine, Hahnemann Medical College and Hospital, and the Bailey Thoracic Clinic.

*Sanborn Company.

TABLE I

	Atrial Septal Defect	Ventricular Septal Defect
Age: range	2 wks. - 61 yrs.	3 mos. - 52 yrs.
number under 15 yrs.	27	76
number under 5 yrs.	13	39
Sex: male	28	50
female	72	50
Diagnosis CHD made: under 10 yrs.	66	100
over 15 yrs.	32	0
No symptoms	5	11
Fatigue	87	72
Shortness of breath	90	70
Cardiac failure	43	22
Chest pain	28	13
Cough	13	12
Paroxysms of rapid heart action	36	8
Hemoptysis	8	6
Syncope	18	6
Failure during pregnancy	2 in 38	0 in 8
Subacute bacterial endocarditis	3	0
Cerebral vascular accident	4	2
Pneumonia	26	33
Physical examination: cyanosis	13	29
thoracic asymmetry	25	52
thrill	25	65
cardiac enlargement	38	46
accentuated P_2	86	68
systolic murmur	92	98
diastolic murmur	28	18
no murmur	4	1
Electrocardiogram: RV hypertrophy	53 of 91	54 of 91
Right bundle branch block	20	3
RVH plus R.B.B.B.	5	0
X-ray: Heart size 2 plus or over	64 of 92 (68%)	50 of 98 (51%)
Pulm. vasc. marks 2 plus or over	64	64
Main pulm. artery 2 plus or over	66	56 of 96
R & L branches 3 plus or over	26	2
RV in RAO enlarged 2 plus or more	53	45
Catheterization: R-L shunt	24	34
Av. R-L shunt	0.7 l/min.	1.2 l/min.
Av. L-R shunt	5.5 l/min.	2.3 l/min.
Pulm. hypertension	65	72
equals systemic	8	48

TABLE II
AGE DISTRIBUTION OF ONE HUNDRED PATIENTS WITH ATRIAL SEPTAL DEFECT

Birth to 1 year	7
1 to 5 years	6
5 to 10 years	8
10 to 15 years	7
15 to 20 years	7
20 to 25 years	7
25 to 30 years	13
30 to 35 years	4
35 to 40 years	13
40 to 45 years	16
45 to 45 years	7
50 to 55 years	4
Over 55 years	1

capacitance electromanometer for pressure determination.* Oxygen determinations were made according to the method of Van Slyke and Neill.[2] Pressure was recorded continuously as the catheter tip was withdrawn from pulmonary capillary bed to vena cava, except at the time a blood sample was being drawn. Routinely, at least three samples were secured in the pulmonary circuit, three in the right ventricle, three or four in the right atrium and one or more from each vena cava. Systemic pressure was measured by cannulation of the brachial or femoral artery and an arterial blood sample drawn. Oxygen consumption was measured whenever possible.

Angiocardiography was performed by injection of the radiopaque substance into the right atrium through an aortography catheter.

At the time of operation, information was gained concerning the atrioventricular valves, the pulmonary veins and both cardiac septa.

Results

History: It is noteworthy that a diagnosis of heart disease was not made before the age of 10 in 34 patients; 17 were 25 or older when they first learned of a cardiac ailment.

Five had no symptom. Two were adults; the others four, eight and 15 years of age.

Eighty-seven complained of fatigue. This ranged in severity from a consciousness of tiring sooner than contemporaries to the inability to walk more than 20 to 30 feet without resting.

Shortness of breath was a complaint of 90. This, too, varied in severity. Paroxysmal nocturnal dyspnea and orthopnea were common among the adult patients.

Chest pain was present in 28, varying in degree and in frequency of occurrence. In three there was radiation down the left arm. There was no constant connection with effort.

Paroxysms of rapid heart action were present in 36. As a rule they were of brief duration, although in two they were so frequent and severe as to be incapacitating.

Thirteen had chronic, non-productive cough. Hemoptysis had occurred at least once in eight. Cyanosis had been present at some time in 13; in three it had appeared late in life. Eighteen had experienced at least one episode of syncope. Twenty-two perspired profusely even in cool weather.

Seven had had one symptom; 15, two; 27, three; 25, four; 11, five; 10, six.

Poor weight gain in infancy was present in 17 and motor development had been retarded in 18. For the majority of the group this information was not available.

Cardiac failure had occurred at least once in 43 patients in all age groups. In a small number it was chronic.

Subacute bacterial endocarditis was known in three. Twenty-four stated that they had had rheumatic fever in the past. Twenty-six had had pneumonia on one occasion; three had had two or more attacks. Four had suffered cerebral vascular accidents; in one the process occurred at the completion of cardiac catheterization.

Twenty-four women had a total of 47 pregnancies. Thirty were normal. Four were complicated by congestive heart failure and one by the onset of paroxysmal atrial tachycardia. The remaining 12 ended in miscarriage.

Physical Examination: Cyanosis was found in 13. In only four was it readily apparent. Scleral suffusion was absent.

Prominent pulsations of the carotids was seen in five, jugular engorgement in three.

The thorax was asymmetrical in 25. Not only was the left anterior chest more prominent than the right but the sternum was frequently bowed outward.

TABLE III
DIAGNOSTIC METHODS EMPLOYED

Catheterization	100
and surgery	46
and angiocardiography	4
and autopsy	3
surgery and angiocardiography	1
surgery and autopsy	10
surgery, angiocardiography and autopsy	2

Thirty-eight presented evidence of cardiac enlargement: widening of the area of cardiac dullness or displacement laterally of the apical impulse.

A thrill was present in 25, systolic in all but one who had a diastolic thrill at the apex. In the others it was located at the point of maximal intensity of the systolic murmur.

Atrial fibrillation was present in seven, gallop rhythm in five. Premature ventricular contractions were of frequent occurrence in the group.

The pulmonic second sound was normal in 12, very faint in two, accentuated in 86.

In four no murmur was audible. In 56, a systolic murmur, alone, was present. It was best heard at the second left interspace in three; the second and third in 13; the third in 15; the fourth in seven; the third and fourth in eight; the second, third and fourth in two; the fifth and sixth in two; the apex in one; along the entire sternal border in four; the fourth right interspace in one. Two distinct systolic murmurs were heard in 12, one at the apex and the other at the second and third (five), the third (six) and the fourth (one) left interspaces near the sternal border.

An early diastolic murmur at the base to the left of the sternum was present in seven, an early or mid-diastolic murmur at the apex in six and a mid-late diastolic murmur with pre-systolic accentuation in three. In all these individuals there was a systolic murmur at the base.

Eight patients had a systolic and an early diastolic murmur at the base, with an additional apical systolic murmur. One had a systolic murmur and an early diastolic murmur at the base, a systolic murmur and a mid-diastolic murmur at the apex. Three had only a diastolic murmur; in each case it was early and located in the second and third left interspaces.

In the majority of instances, the systolic murmur at the base was transmitted over the left anterior and posterior thorax. In a smaller number it could not be heard posteriorly. In others it was transmitted only along the left sternal border, and in three it was well localized.

Moderate clubbing of the digits was present in three with cyanosis. Two, both very young, had erythema of the skin over the distal phalanges.

Non-cardiac anomalies in the group included pectus excavatum, strabismus (two), diastasis recti and undescended testes, Mongolism, double nipple, and multiple defects of skin and muscle (two).

The Electrocardiogram: Nine tracings were either incomplete or missing. Ninety-one were studied. Five were normal. Two patients exhibited the Wolf-Parkinson-White phenomenon. Ten tracings showed first degree atrioventricular block. The majority of patients had right axis deviation; however, three with right bundle branch block and two with right ventricular hypertrophy pattern had left axis shift, and eight with right ventricular hypertrophy had no axis deviation. Fifty-three (58 per cent) had definite criteria of right ventricular hypertrophy. Twenty (21 per cent) had right bundle branch block. Five had tracings suggestive of both right bundle branch block and right ventricular hypertrophy.

Roentgen Examination: Because fluoroscopic observations could not be rechecked, they are not considered. They agreed fairly closely with film interpretation, however. In the majority of patients, pulmonary vascular pulsations were prominent.

Three showed no abnormality. Pulmonary vascular markings were definitely increased in 85 and the main pulmonary artery dilated in 81. The prominence of these structures was graded two plus or greater in 65 and 67, respectively. The right and left branches of the pulmonary artery were dilated in 62, being three plus or greater in 28.

The heart was enlarged in 83, varying from one plus to five plus. In 67 it was two plus or larger. The increase in mass was almost invariably to the left.

The apex was depressed in nine. In the remaining the left border was almost invariably rounded, with or without appreciable elevation of the apex.

Right atrial enlargement was found difficult of assessment. In 14 there seemed to be little doubt that the right inferior cardiac segment was abnormally prominent in the postero-anterior view. In five there was posterior inferior prominence in the right anterior oblique view.

Seventy-nine showed evidence of right ventricular enlargement in the right anterior oblique position. In 56 this was two plus or greater.

The aorta appeared normal in all cases in which it was visualized. In two there was visible calcification in the pulmonary artery. Twenty-seven had scoliosis of the thoracic spine. Representative postero-anterior films are shown in Fig. 1.

Cardiac Catheterization: The highest step-up in oxygen content from the vena cavae (average) to right atrium (average) was 8.9 volumes per cent. The left to right shunt through the defect ranged between 0 and 19 liters per minute; the right to left shunt between 0 and 1 liter/minute. Twenty-five had definite arterial unsaturation.

Pulmonary artery and right ventricular hypertension (systolic pressure of more than 30 mm. Hg.) was present in 65 individuals, being over 50 mm. in 52. In only eight were pulmonic and systemic systolic pressures of the same order of magnitude.

There was a definite correlation between the amount of blood shunted from left to right and the pulmonary pressure: the lower the pressure the greater the shunt.

The catheter passed from right atrium to left in 25. In 14 there was a definite gradient in mean pressure from left to right, ranging between 1 and 10 mm. Hg. In two, right atrial mean pressure was higher than left. In the rest the two were equal.

In 13 a pulmonary vein was entered. In each there was a definite gradient in mean pressure from vessel to atrium, ranging between 1 and 8 mm. Hg.

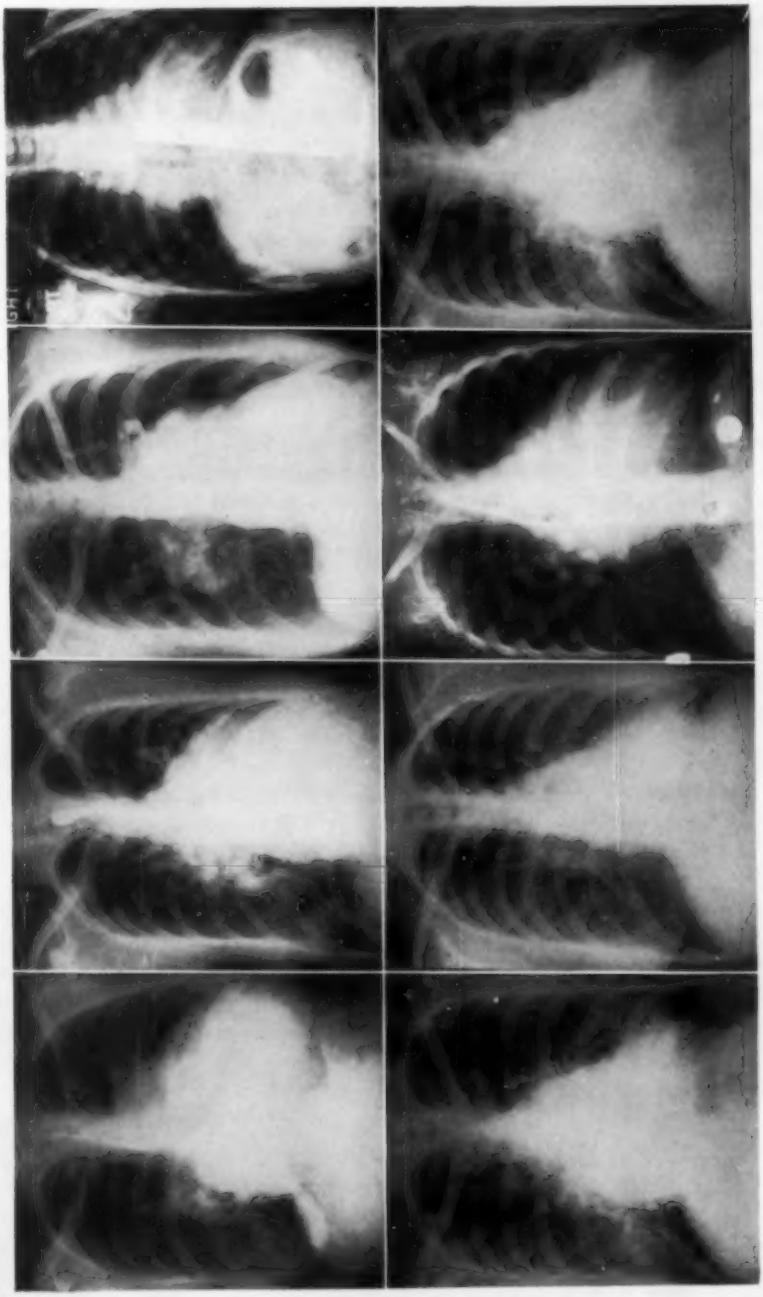

FIGURE 1: Atrial septal defect. Representative postero-anterior roentgenograms.

A persistent left superior vena cava was entered on five occasions, each time by way of the coronary sinus so far as could be determined.

Angiocardiography: In the seven studies performed, simultaneous opacification of right and left atria before the contrast substance reached the pulmonary circuit was seen on five occasions.

Operation and Autopsy: By these means the site of the defect was determined in 62 patients. The septum secundum was alone involved in 43, the septum primum in 12, and both areas in three. Multiple defects were present in two and virtually the entire septum was absent in two.

The presence of anomalous pulmonary vein drainage was demonstrable in 12. Either one or two veins from the right lung entered the right atrium of 8 patients, the superior vena cava of 3 and both areas in 1.

Discussion

This series is similar to others in that there is a definite sex predilection for atrial septal defects, 72 per cent of these patients being female.

The age distribution of the group is worthy of comment. Only 28 were under 15 years of age. This is in distinct contrast with our observations in other lesions. A review of the senior author's experience in other hospitals further serves to establish the fact that the lesion is demonstrated by catheterization relatively infrequently in the young. This may indicate that the defect is silent in many individuals during childhood. No murmur is heard and, therefore, the child is not referred for evaluation. The fact that a diagnosis of heart disease was not made until after the age of 10 in 34 of these patients (in 17, only ofter 25 years) is probably significant of something more than inferior medical care in earlier years.

Fatigue and shortness of breath, as would be expected, were the chief symptoms. In almost every instance, one or the other was the initial indication that all was not well. They were present in all except three of the patients under 15 years of age and one or the other had been noted during feeding in early infancy or since the time of ambulation. The adult patients, on first questioning, dated their appearance to a period of late life, usually maintaining that they were in excellent health until a relatively few years previous to coming under our observation. However, when given time to reflect, a large number recalled that during childhood they could not keep up with their fellows. Others would admit restriction of physical activity, imposed or voluntary, throughout life, indicating that the lack of symptoms might have been for want of a test of stamina.

Paroxysms of rapid heart action were next in frequency. In a small number this was the first symptom. As a rule the episodes could not be terminated by vagal stimulation.

Congestive heart failure was common, having been present in 43. Seven of these were children. In all probability, decompensation had occurred in a larger number. We make this statement because of the frequency with which a normal temperature had been associated with a diagnosis of pneumonia in many of the group. We are convinced that one reason for the

oft-repeated view that atrial septal defect is commonly complicated by pneumonia is the improper interpretation of signs of heart failure.

Disturbances in growth and development have been assumed to be common manifestations of the anomaly. In this series, although a positive history of retardation in infancy was secured in a small number, there was no evidence from physical findings of a characteristic habitus. Even those patients most severely affected were of normal development as a rule.

We, as well as others, have stated in the past[3] that rheumatic carditis is more frequent in cases of atrial septal defect than in any other congenital heart lesion. On the basis of an experience broader than when this statement was made, we now feel that although this may be true, it is of little statistical importance. Although 24 patients gave a history of rheumatic fever at some time in the past, only a few had had symptoms or signs suggestive of this state. It appears that in most instances the diagnosis was made merely because a murmur was discovered. We were able to demonstrate anatomic evidence of rheumatic involvement in three patients. Two had mitral stenosis and the other both mitral and aortic stenosis. Two additional individuals, not included in this series, have been shown to have mitral stenosis. Considering our entire experience, the incidence is not high. In all probability the diagnosis of atrial septal defect and rheumatic valvular involvement is made so frequently only because the diastolic murmur commonly found with the uncomplicated defect has been misinterpreted.

Subacute bacterial endocarditis occurred in three of our patients. We had been led to believe that it is of extreme rarity in this condition, being much more common in ventricular septal defects. In our group of 100 cases of ventricular septal defect, however, no single instance was recorded.

Atrial septal defects are usually thought of in connection with cerebral vascular accidents due to emboli from the right heart. Four patients in this group had such accidents, while two in the ventricular septal defect series had suffered the catastrophe. Probably the danger of the event is little greater in the one than the other.

The two constant physical findings accompanying the defect are accentuation of the second sound at the base to the left of the sternum and a systolic murmur. The murmur is not characteristic. It may be heard best in any interspace along the left sternal border and has varied as widely as that of the murmur accompanying ventricular septal defects. The genesis of the murmur is not clear. It may well be due to flow of blood across a pulmonary valve of normal size into a dilated pulmonary artery. In a few of our patients the thrill felt over the pulmonary artery at the time of surgery disappeared following closure of the defect. The presence of secondary systolic murmurs and of diastolic murmurs may be explained on the basis of the mechanism offered for similar murmurs in ventricular septal defect.

The electrocardiogram is of some value in the clinical diagnosis. Right bundle branch block is of frequent enough occurrence that its presence

in a patient with other, compatible signs allows a tentative diagnosis to be made. This does not, however, excuse the omission of definitive study. The relationship of pulmonary and right ventricular hypertension to the patterns of right ventricular hypertrophy and of right bundle branch block is of interest. Seven individuals with right ventricular hypertrophy had normal right heart pressure; 46 had hypertension. Thirteen with right bundle branch block had normal pressure, seven had hypertension. It would appear that, as a rule, the greater the burden on the right ventricle the more likely the appearance of a hypertrophy pattern.

The single most striking observation in reviewing the x-ray films was the large size of the right and left branches of the pulmonary artery. It may be safe to say that in any group of individuals with congenital heart disease and large main pulmonary artery branches, the majority will have atrial septal defects. Large flows over a long period of time are possible in this malformation. Again, this is merely suggestive and does not excuse omission of complete study.

Comparison of the catheterization data in this series with those of the group with ventricular septal defects makes it clear that larger left-to-right shunts exist in atrial septal defects and that pulmonary artery pressure tends to be much lower. In explaining the hypertension developing in ventricular septal defects the following hypothesis was offered: as a result of increased flow of more highly oxygenated blood through the pulmonary circuit, there occurs functional constriction of the small pulmonary vessels. To sustain the contraction, hypertrophy of the medial elements takes place. The narrowing of vessel lumina which results leads to increased resistance to flow and induces a rise in pressure proximally. The hypertension is traumatic to the intima and results in thickening, thus further narrowing the lumina. A cycle is instituted which makes for progressively greater resistance to flow, more severe hypertension and progressive diminution in the left to right shunt.[1]

If this proposition is valid, why, then, is there not seen the identical process in atrial septal defect, in which the same causative mechanism is present and in which the left to right flow is actually greater? The answer to the objection is that the process in the two conditions *is* identical but the rate of change differs. The necessity for alteration in the caliber of pulmonary vessels is more immediate in ventricular septal defect.

Let us consider the situation existing in each defect with the supposition that pulmonary vessels are of normal caliber and resistance to pulmonary flow is not increased.

A defect in the wall between the two atria allows a flow from left atrium to right. The shunted blood is delivered at a relatively low pressure into a distensible chamber, in great part during ventricular systole. Although the minute output of the right ventricle must be increased to circulate the additional load, the stroke volume is limited by the capacity of the atrial chamber. In other words, with the onset of ventricular systole, the limit of increase in pulmonary flow has been reached because no more

blood is delivered from the atrium. On the other hand, a defect of significant size in the wall between the two ventricles, allowing a shunt in the same direction and during the same portion of the cardiac cycle, will result not only in an increase in minute volume of the right ventricle but also one in stroke volume which is limited only by the capacity of both ventricles. The chamber has been filled by blood from the right atrium and contracts. The left ventricle, filled from the left atrium, contracts at the same time. Its content is allowed two directions of flow: into the relatively high resistance aortic circuit or into the low resistance pulmonic circuit. The law stating as it does, the blood will seek the path of least resistance and will traverse the defect, in greater or less amount depending on its size, to the pulmonary artery. Thus, pulmonary flow would be much greater than in the case of an atrial defect because systemic output could be almost completely diverted to the pulmonary system. Therefore, the impetus for changes in the pulmonary vascular bed would be of maximum potential and their prompt appearance necessary to protect life.

Treatment

The results of surgery and the techniques used in many members of this series have been previously described[3, 4] and require no repetition. However, because our criteria as to operability or inoperability stem in part from this study, that aspect of the treatment merits comment. In addition, the pre-operative diagnosis of the location of the defect must be discussed.

The purpose of any surgical procedure designed to close an atrial septal defect is to remove the extra load placed on the right ventricle and thus to prevent cardiac failure and premature death. The increased work of the right ventricle results from two things: an amount of blood in excess of normal which it must pump to the lungs and an increase in the resistance which it must meet in order to pump the blood. Obviously, then, the desirability of surgical closure depends upon the magnitude of the left to right shunt and upon pulmonary pressure.

From our studies it develops that the greater the pulmonary resistance, the less the left to right shunt. A point is reached when such a shunt becomes impossible because of tremendous resistance. Later, the diastolic capacity of the right ventricle having decreased due to hypertrophy of the wall, right atrial pressure rises and now there is instituted a right to left shunt. Inasmuch as the only manner in which a surgical procedure can alter the dynamics in this malformation is by preventing a shunt, closure of the defect in a patient who no longer has a left to right shunt will do nothing to decrease right ventricular work. Closure in a patient who has a chronic right to left shunt will actually increase right heart strain because there is no longer a route for decompression of the right atrium.

These theoretical considerations have given weight by our practical experience with surgery in 82 individuals, in 70 of whom the atrio-septo-

pexy operation was used. There is a direct relationship between mortality and morbidity and the magnitude of pulmonary hypertension. As a result we have arrived at a classification of victims of the defect in regard to surgery.

Class I. Patients with a significant left to right shunt (2 l/min. or more) and normal pulmonary pressure. These are the ideal candidates. An adult in this group should be operated upon. No one can predict when pulmonary vascular changes will be initiated and how quickly they will progress. Only because of technical difficulties at the present time, an infant or young child should be allowed to reach an adequate size.

Class II. Patients with a significant left to right shunt and minimal or moderate pulmonary hypertension. These individuals require surgery, whether or not they have symptoms. Their condition will never be better than it is but may become worse at any time, thus decreasing the chances of surviving operation.

Class III. Patients with a small left to right shunt and marked pulmonary hypertension. Surgery in this group is urgently necessary. Closure of the defect will decrease right ventricular work, and perhaps the pulmonary vascular changes may be to some extent reversible.

Class IV. Patients with no shunt and marked pulmonary hypertension. We consider that these have presented themselves too late. As a rule, the procedure itself requires more than their reserve and they die in the operative period. In those who have survived we have been unable to demonstrate any physiologic improvement. It remains to be seen whether a significant number may be salvaged. Perhaps under normal conditions there is still a small left to right shunt which cannot be demonstrated by catheterization. We can hope that in these the pulmonary vascular changes will in time regress or remain stationary so that a longer life is possible.

Class V. Patients with no left to right shunt, a right to left shunt and marked pulmonary hypertension. Surgery in these patients is contraindicated. We feel that this holds true also for those who have a small shunt in both directions. The burden on the right ventricle is due now entirely to increased pulmonary resistance and closure of the defect could be expected to be lethal.

The most pressing problem confronting those who must choose patients for operation is the determination of the location of the defect; specifically, whether or not there is at least a small rim of septal tissue above the atrio-ventricular valves. If there is no tissue in this area, closure of the defect is extremely hazardous because of the possibility of injuring conduction tissue or of destroying the integrity of either of the atrio-ventricular valves which lie so close. We must confess that to date we have not discovered the solution. In those cases in which the location has been determined we have considered the following factors: history of heart failure, location and time of murmur, roentgen features, axis deviation, presence of right ventricular hypertrophy or right bundle branch block, mag-

nitude of left to right shunt, and degree of pulmonary hypertension. No single factor and no combination of factors is of significance in localization of the defect. Unfortunately, once it has been determined that closure of an atrial septal defect is desirable, surgical exploration remains the sole method of discovering whether or not it should be attempted.

SUMMARY AND CONCLUSIONS

One hundred consecutive patients in whom an atrial septal defect was demonstrated and who were studied by right heart catheterization have been analyzed.

The malformation produces symptoms in the majority of patients. Cardiac failure is common.

The most characteristic roentgen feature is the presence of marked dilatation of the left and right branches of the main pulmonary artery. This is seen much less frequently in other lesions allowing a left to right shunt.

The electrocardiogram shows evidence of right ventricular hypertrophy in a majority. Right bundle branch block is less than one-half as common.

Although pulmonary hypertension is found very frequently, the pressure tends to be lower than it is in ventricular septal defects. The left-to-right shunt, on the other hand, tends to be greater.

The mechanism of development in both atrial and ventricular septal defects of pulmonary hypertension is the same. However, initial and potential flow through a defect in the interventricular septum is greater than that through one of similar size in the atrial septum. The stimulus to pulmonary vascular changes is greater and the necessity more acute in the former.

There are no characteristic historical or physical findings. Although right bundle branch block and marked dilatation of the primary branches of the pulmonary artery in a patient with a systolic murmur at the base allows one to be very suspicious of the presence of an atrial septal defect, the diagnosis depends upon cardiac catheterization.

Patients may be divided into five classes so far as the desirability of surgical closure is concerned. The magnitude and direction of shunt through the defect and the height of pulmonary pressure are the basic considerations.

Defects in the septum just above the atrio-ventricular valves are extremely difficult to close if there is not at least a small rim of septal tissue in the area and the attempt is greatly hazardous. Unfortunately, at the present time only surgical exploration allows diagnosis of the anatomic conditions.

RESUMEN Y CONCLUSIONES

Se han analizado cien pacientes consecutivos en los cuales se demostró una malformación septal del atrio y que fueron estudiados por cateterización de corazón derecho.

La malformación presenta síntomas en la mayoría de los pacientes. La insuficiencia cardiaca es común.

La característica radiográfica más notoria es la presencia de dilatación marcada de las ramas izquierda y derecha de la arteria pulmonar principal. Esto se ve con mucho menor frecuencia en otras lesiones que permiten un corto circuito de izquierda a derecha.

El electrocardiograma presenta evidencia de hipertrofia ventricular derecha en la mayoría. El boqueo de la rama derecha del haz de his es menos frecuente que en el 50%.

A pesar de que se encuentra hipertensión arterial muy frecuentemente la presión tiende a ser menor que en las malformaciones septales ventriculares. El corto circuito de izquierda a derecha, en cambio, tiende a ser mayor.

El mecanismo del desarrollo de la hipertensión pulmonar en ambas malformaciones septales, del atrio y del ventrículo, es el mismo. Sin embargo el flujo inicial y potencial a través de la malformación en el septum interventricular es mayor que en uno de igual tamaño en el septum del atrio. El estímulo a los cambios arteriales pulmonares es mayor y la necesidad más aguda que en el anterior.

No hay hallazgos característicos en la historia o en la exploración física. A pesar de que el bloqueo de rama derecha y la dilatación marcada de las ramas primarias de la arteria pulmonar en un paciente con murmullo sistólico en la base permite sospechar la existencia de un defecto septal del atrio, el diagnóstico depende de la cateterización.

Los pacientes se pueden dividir en cinco grupos de acuerdo con la necesidad de cierre quirúrgico. La magnitud y la dirección del corto circuito a través de la malformación y la altura de la presión pulmonar son las consideraciones básicas.

Los defectos en el septum inmediatamente por encima de las válvulas auriculo-ventriculares son extremadamente difíciles de cerrar si no hay por lo menos un pequeño borde de tejido septal en el área y el intento es muy arriesgado. Desgraciadamente en la actualidad solamente la exploración quirúrgica permite el diagnóstico de las condiciones anatómicas.

RESUME

Les auteurs rapportent une étude portant sur cent malades atteints d'anomalies du septum auriculaire chez lesquels fut pratiqué le cathétérisme du coeur droit.

L'anomalie septale engendre des symptômes pour la majorité des malades. L'insuffisance cardiaque est commune.

L'élément radiologique le plus caractéristique est la présence d'une dilatation marquée des branches gauche et droite de l'artère pulmonaire. Cette constatation est beaucoup moins fréquente dans les lésions provenant d'un shunt de gauche à droite.

L'électrocardiogramme met en évidence dans la majorité des cas une hypertrophie du ventricule droit. L'existence de troubles du rythme par atteinte septale est moitié moins commune.

Bien que l'on constate très fréquemment une hypertension pulmonaire, la pression tend à être plus basse que dans les anomalies du septum ven-

triculaire; d'autre part, le shunt de gauche à droite se rencontre plus souvent.

Le mécanisme du développement de l'hypertension est le même dans les anomalies septales des oreillettes et des ventricules. Cependant la puissance du flot sanguin est plus grande quand il s'agit d'une malformation de la cloison interventriculaire que lorsqu'il s'agit d'une malformation de dimension semblable de la cloison de l'oreillette. L'action fâcheuse sur les vaisseaux pulmonaires est plus importante dans le dernier cas.

Il n'y a aucune constatation historique ou physique caractéristique. Bien que l'existence de troubles du rythme ventriculaire et d'une dilatation nette des premières branches de l'artère pulmonaire chez un malade, accompagnée d'un murmure systolique à la base permettent d'être très circonspect en présence d'une déformation septale de l'oreillette, le diagnostic dépend du cathétérisme cardiaque.

Les malades peuvent être divisés en cinq classes selon la nécessité d'une fermeture chirurgicale. L'amplitude et la direction du shunt à travers la malformation et le niveau de la pression pulmonaire sont les considérations de base.

Les déformations de la cloison siégeant immédiatement au-dessus des valvules atrio-ventriculaires sont extrêmement difficiles à fermer s'il n'y a pas au moins un petit rebord de tissu septal dans la région; la tentative est alors très audacieuse. Malheureusement à l'heure actuelle, seule l'exploration chirurgicale permet de préciser l'état anatomique.

ZUSAMMENFASSUNG UND SCHLOSSFOLGERUNGEN

Es wird über 100 Patienten, bei denen ein Vorhof-Septum-Defekt nachgewiesen und eine Katheterisierung des rechten Herzens vorgenommen wurde, berichtet.

Die Missbildung verursachte bei den meisten Patienten Symptome; Herzbeschwerden sind immer vorhanden.

Das charakteristischste röntgenologische Merkmal ist die deutliche Dilatation der rechten und linken Äste der Pulmonalarterie. Bei anderen Herzfehlern mit Links-Rechts-Shunt wird diese Veränderung seltener beobachtet.

Das Elektrokardiogramm zeigt meistens eine Hypertrophie des rechten Ventrikels. Ein rechtsseitiger Schenkelblock kommt nur halb so häufig vor.

Obgleich ein pulmonaler Hochdruck sehr häufig gefunden wird, sind die Druckwerte meist niedriger als beim Ventrikel-Septum-Defekt. Andererseits neigt der Links-Rechts-Shunt zur Vergrösserung.

Der Entwicklungsmechanismus des pulmonalen Hochdruckes ist beim Vorhof- und Ventrikel-Septum-Defekt der gleiche. Bei dem Ventrikel-Septum-Defekt ist jedoch der initiale und potentielle Shunt grösser als der bei einem gleich grossen Defekt im Vorhofseptum. Bei dem ersteren sind Lungengefässveränderungen häufiger, und ihr Auftreten ist zwangsläufiger.

Es gibt keine charakteristischen anamnestischen Symptome und klinischen Befunde. Obwohl rechtsseitiger Herzblock und deutliche Dilata-

tion der primären Äste der Pulmonalarterie bei Patienten mit systolischem Geräusch an der Basis den Verdacht auf das Vorliegen eines Vorhof-Septum-Defektes zulassen, ist Herzkatheterismus zur Erhärtung der Diagnose erforderlich.

Hinsichtlich der Notwendigkeit chirurgischer Massnahmen kann man die Kranken in fünf Gruppen einteilen. Dabei kommen als Hauptgesichtspunkte Grösse und Richtung des Shunts sowie die Höhe der pulmonalen Hypertrophie in Frage.

Der Verschluss unmittelbar über den Atrio-Ventrikulärklappen gelegener Septum-Defekte ist sehr schwierig und riskant, wenn nicht wenigstens ein schmaler Rand von Septumgewebe in diesem Gebiet vorhanden ist. Unglücklicherweise ist die Feststellung der genauen anatomischen Verhältnisse gegenwärtig nur durch chirurgische Massnahmen möglich.

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Pulmonary Brucellosis

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Brucellosis is one of the most important of the new diseases discovered in recent times by bacteriological methods, and should be considered early in the diagnosis of an obscure illness. It is unfortunate there is no one reliable, specific test generally available for the diagnosis. In the diagnosis of brucellosis, the finding of Brucella by blood culture is diagnostic, but the test requires careful and rigid technique not available to that great group of practitioners most likely to observe the early cases. Then, too, the obtaining of a positive culture is largely a matter of accident in acute brucellosis and rarely found in chronic brucellosis. We should emphasize that negativity of any one test does not necessarily indicate that a Brucellar infection is not present, either in acute or chronic pulmonary brucellosis. A number of these diagnostic discrepancies may be mentioned. The agglutination test is of significance, only, if positive. A positive intradermal reaction indicates increased sensitivity to Brucella antigen but does not signify whether the infection is active; on the other hand, negative reactions have been observed in acute Brucella infections with positive blood cultures. The opsonocytophagic test requires accurate technique with virulent Brucella organisms. Increased phagocytosis with a positive intradermal reaction suggests a still active infection, although it may be logical to infer that a high degree of phagocytosis implies a balance between infection and immunity, but it does not mean that a Brucella infection is not present. Conditions, such as stated, produce a situation seemingly impossible for solution, but it is my opinion a diagnosis can be made in a large percentage of the cases observed. I shall attempt to enlarge and elucidate on these problems later in this discourse.

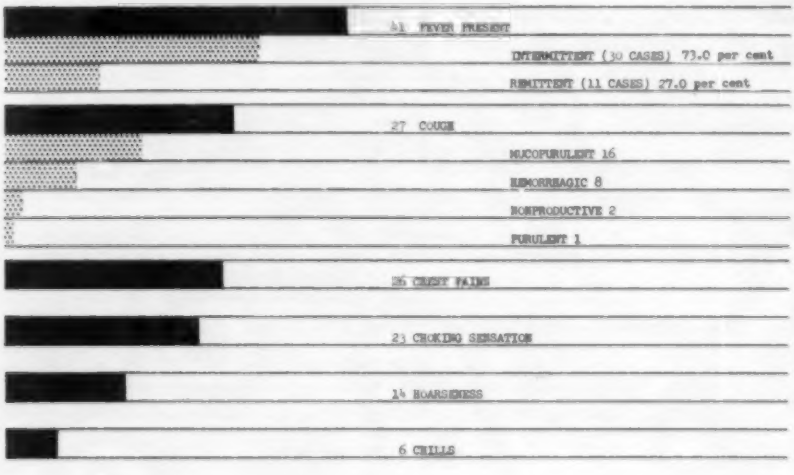
The too great tendency of physicians to tell their patients they have recovered after several weeks treatment of the acute type, or a short term of therapy in the chronic phase, is wrong. We cannot be certain that such patients have recovered or might relapse into the chronic type of brucellosis. Their apparent immunity may or may not be due to a low-grade, subclinical infection, localized in the hilar and mediastinal lymph nodes, small nodularities within the pulmonary parenchyma or elsewhere in the body. I would not go so far as to state that continuing skin sensitization to Brucella denotes an active, subclinical infection, but to declare no infection is present may be equally fallacious, especially if opsonification is present as well. The burden of proof whether a Brucellar infection is present should rest upon the attending physician to properly interpret all the available data—history, clinical symptomatology, differential diagnostic procedures, in conjunction with relative evaluation of the intradermal, agglutination and opsonocytophagic tests, blood culture if available, combined with mature, unbiased clinical knowledge and judgment. There

seems to be a group of medical observers who believe a positive blood culture is the sine qua non in the diagnosis of brucellosis. This is, in my opinion, an overstatement and from a practical viewpoint not justifiable. If this conception were correct and persons with chronic brucellosis were allowed to progress without a definitive diagnosis and adequate treatment for years, they might be diagnosed improperly as neurasthenia, psychoneurosis, tuberculosis, chronic arthritis, subacute cardiac infection, et cetera.

This presentation consists of two parts, namely, (a) a survey of 41 cases of pulmonary brucellosis obtained from 13 physicians in answer to a questionnaire sent to 700 chest specialists throughout the United States, (b) an analytical report of 27 cases of pulmonary brucellosis, not previously published, consisting of 18 cases of my own and nine from the United States Veterans Hospitals at Louisville, Kentucky, and Houston, Texas. The latter nine cases were selected because their histories, laboratory data and x-ray films were available to me for detailed analysis. One hundred eighty-seven (187) of 700 selected chest specialists answered my questionnaire; only 13 (1.8 per cent) of the 700 reported observed patients with pulmonary brucellosis, and from this group of 13 (11 acute, 30 chronic) cases were obtained.

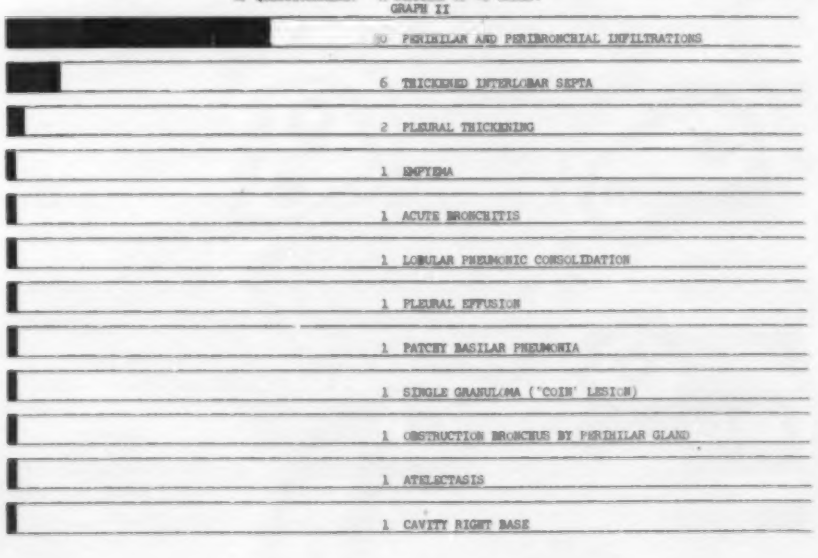
It is evident these 13 physicians observed a high percentage of pulmonary pathology in comparison to the small percentage of the entire group to whom the request was made. It is assumed that the physicians, who failed to answer my inquiry, presumably had no data nor cases to report. At any rate, it indicated either an unawareness of the disease or the lack of it in their areas. Cough with mucopurulent or hemorrhagic sputum was frequently observed. The prominent symptoms (Graph I) were

SUMMARY OF SIMPTOMS FROM ANALYSIS OF QUESTIONNAIRE.
A SUMMARY OF 41 CASES
GRAPH I



in order of frequency, fever, cough and chest pains, choking sensations, hoarseness, arthritic pains, and chills. The duration from the onset of their illness to the time of diagnosis was from six days to six months. The physical findings in the chest, except in some of the acute cases, were of slight importance. A large group (92.3 per cent) was composed of farmers, ranchers and packing house workers, and the occupation of 7.7 per cent had no direct relationship, either to cattle, sheep or swine. Thirty-six (36) infections were caused by Br. abortus, three to Br. melitensis, and two to Br. suis; the latter five cases being mostly acute types. A positive blood culture was obtained in eight acute cases, negative or not made in the remaining 33 patients. The intradermal test was performed in most cases. The opsonocytophagic test was made in 23 patients with an average Modified Foshay index of 56. The blood count showed a moderate anemia, tendency toward lymphocytosis, and a sedimentation rate slightly to considerably increased but of little value. The x-ray findings (Graph II) in the acute cases revealed bronchopneumonia in eight, acute bronchitis, pneumonitis, and pleural effusion (later empyema) in one each; the chronic cases showed perihilar thickening and peribronchial infiltrations in 30 patients, including, as well, pleural thickening in two, thickening interlobar septa in six, a single granuloma ("coin" lesion) in one, and obstruction of a bronchus with ensuing atelectasis, caused by encroachment upon the bronchus by enlarged perihilar nodes in one case. Eleven acute cases were treated as follows, three with surgery (one decortication, one lobectomy, one pneumonectomy), aureomycin and streptomycin being used with the surgery, three with brucellin unsuccessfully, four with aureomycin alone and one combined with streptomycin successfully.

GRAPHIC CHART SHOWING SUMMARY OF X-RAY FINDINGS (AS TO INDIVIDUAL OCCURRENCE) FROM ANALYSIS OF QUESTIONNAIRE. A SUMMARY OF 41 CASES.
GRAPH II



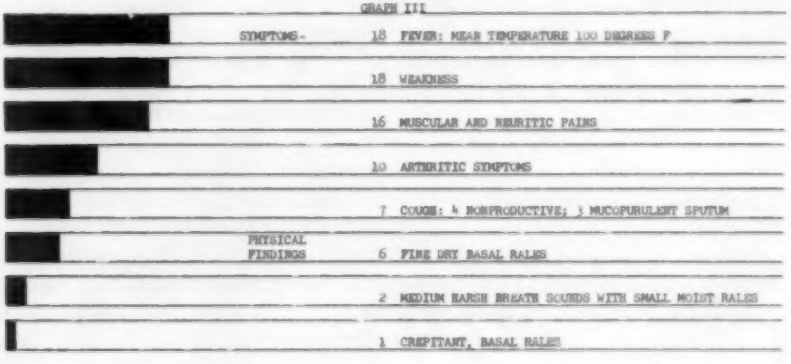
Data regarding the therapy of the chronic cases were not detailed enough to arrive at a definite opinion except that the treatment with brucellin was not objectively successful, either due to its ineffectiveness or other factors such as lack of duration of treatment.

My general impression from the information contained in the questionnaire is the lack of awareness of pulmonary brucellosis per se among specialists in the field of pulmonary disease and I feel justified at this time in reporting this survey as well as the 27 other cases in this article.

In summarizing the nine cases selected from the 41 reported in answer to the questionnaire certain salient observations can be stated. The rather long periods in the acute and chronic cases of brucellosis before a definite diagnosis was made and treatment instituted is noteworthy. The average duration of treatment in four of the acute cases was 19 days, and, moreover, without an ensuing follow-up; this was equally true of the chronic cases. It is possible and likely some of the acute cases may have relapsed, and the one chronic case treated for 14 days with aureomycin most likely relapsed at a subsequent time. Intermittent or remittent fever was present in all cases, averaging 101.8 degrees F., in the acute and 100.2 degrees F., in the chronic cases. The onset of acute brucellosis was initiated most frequently by fever, chills, weakness, cough, dyspnea and headache. Generalized weakness, musculoneuritic pains, neuropsychotic manifestations, joint, digestive and respiratory symptoms were reported. It is interesting to note that nine had respiratory symptoms—dyspnea and cough in eight and one with pleural pain. The physical examination, except in the acute cases, was not informative. The chest x-ray films showed definite pathology, suggesting pneumonitis, pneumonia, localized granuloma, bronchial obstruction by nodes, pleural thickening, marked perihilar thickening and peribronchial infiltrations. The routine blood analysis revealed no anemia, only a moderate, relative lymphocytosis. The blood culture was positive in only one of the four chronic cases in this series. The agglutination test was made routinely, the opsonocytophagic test not at all, the intradermal (Brucellergin) reaction twice only in the nine cases. The treatment in the acute cases appeared to be moderately successful but less so (50 per cent)

GRAPHIC CHART SHOWING SYMPTOMS AND PHYSICAL CHEST FINDINGS OF MY 18 CASES

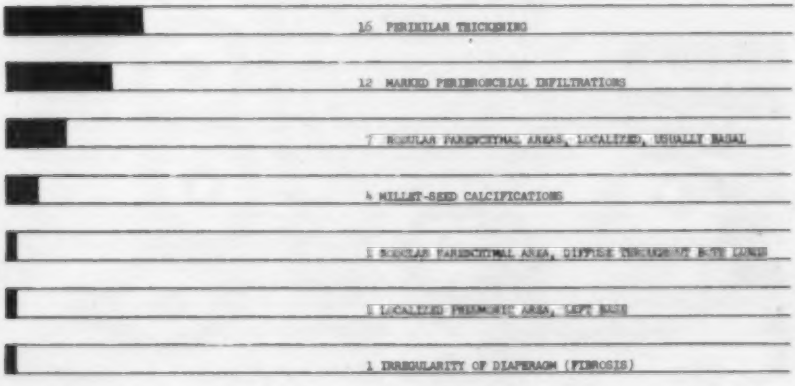
GRAPH III



in the chronic cases.

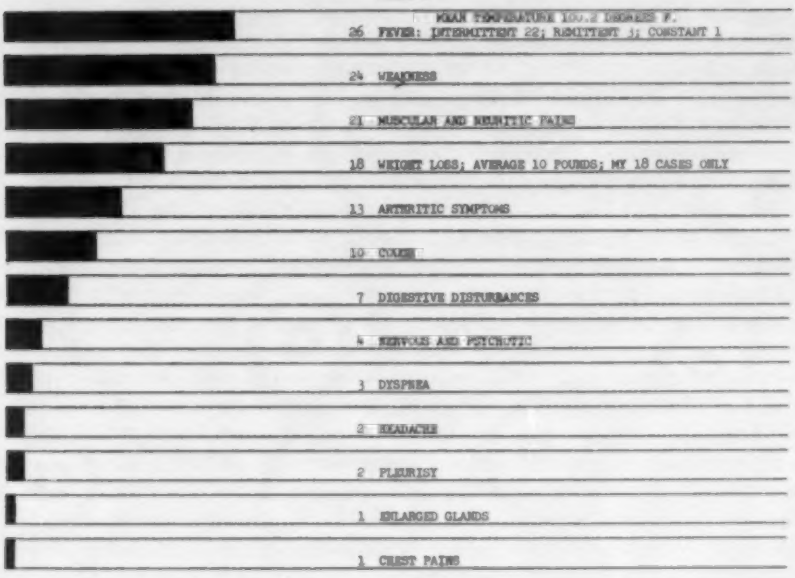
In analyzing the patients with chronic pulmonary brucellosis treated by me, the mean age was 41 years; ratio of women to men 2:1. Six lived on cattle ranches, one was a county demonstration agent in Southwestern Texas; the remaining 11 had no direct connection with cattle, sheep nor swine. There must have been an indirect relationship, however, because all of the 18 individuals lived in Texas where Bang's disease in farm animals is endemic. Their histories reflected they had been ill from three to 108 months with a mean time for the 18 cases of 26 months before an accurate diagnosis was made. Their symptoms at the onset of their initial sickness, months before admission to the Clinic, consisted of intermittent fever, ranging from 101-104 degrees F., joint pains, mainly vertebral, recurrent, generalized aching, fatigue, nervous irritability, minor psychoses, occipital headaches, sweating, chills and gastrointestinal disturbances, such as diarrhea, abdominal pain, nausea and vomiting. At the time of admission to the Clinic the principal complaints (Graph III), in order of frequency were: intermittent fever, ranging from 99 to 101 degrees F., a mean of 100 degrees F.; generalized muscular aching; weakness and easy fatigability; painful joints, usually the vertebrae and large joints (hip, knee, shoulder); cough in two-fifths of the cases, being associated with mucopurulent or purulent sputum; dysuria with slight occasional hematuria in one; an average weight loss of 10 pounds. The physical examination of the chest revealed fine, dry rales in six, harsh breath sounds with small, moist rales in two, and crepitant rales in one; all findings within the basal areas. It was evident the physical examination of the chest was not definitively diagnostic. The routine blood analyses and blood pressure readings were within normal range. The pulse rate was moderately accelerated (mean of 89). The intradermal brucellergin test was uniformly positive with an average reaction of 3-plus. The agglutination test was negative in three and positive in 15 cases, varying in titer from 1:20 to 1:2560 (one case); excluding the one with the high

GRAPHIC CHART SHOWING X-RAY FINDINGS OF MY
18 CASES
GRAPH IV



GRAPHIC CHART SHOWING SUMMARY OF SYMPTOMS OF 27 CASES PULMONARY BRUCELLOSIS, 9 FROM UNITED STATES VETERANS HOSPITALS AND 18 OF MY OWN.

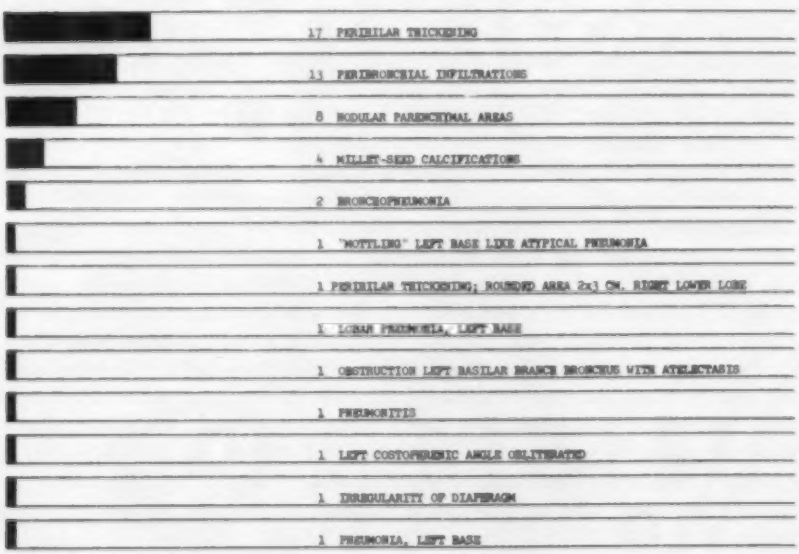
GRAPH V



titer of 1:2560, the mean titer of the other 14 cases was 1:130. The mean opsonification index (Modified Foshay) for the 18 cases was 30. The urinalyses were negative in 16 but in the other two, one who gave a history of renal stone and showed 1-plus albumin and the second case had mild hematuria due to urethral caruncle and trigonitis. We found no glycosuria in any of our patients at any time. The chest x-ray film findings (Graph IV) were interesting and suggestive, revealing in most patients marked perihilar thickening and peribronchial infiltrations and in almost one-half (44 per cent) nodular areas of varying size within the parenchyma of the lung, usually basally localized. One patient had a widespread lung involvement of grayish nodules, both discrete and at times closely conglomerated. In approximately one-half of the series fine, discrete, millet-seed calcifications were noted mainly within the lower pulmonary segments There was one consolidation of medium size in the right lower lobe, which was likely a granuloma, and an irregularity of both diaphragmatic contours in one. The result of therapy with brucellin and antibiotics was quite discouraging in the chronic cases of brucellosis, however, administration of a cobalt-copper-manganese combination resulted in apparent recovery in seven of nine patients so treated. It may be unwise to state with emphasis that these seven had eradicated their infections completely, however, they have remained free of their complaints and appear to be completely recovered from their brucellar infection after months of observation. I do not know and can only conjecture the reasons and rationale for this favorable result.

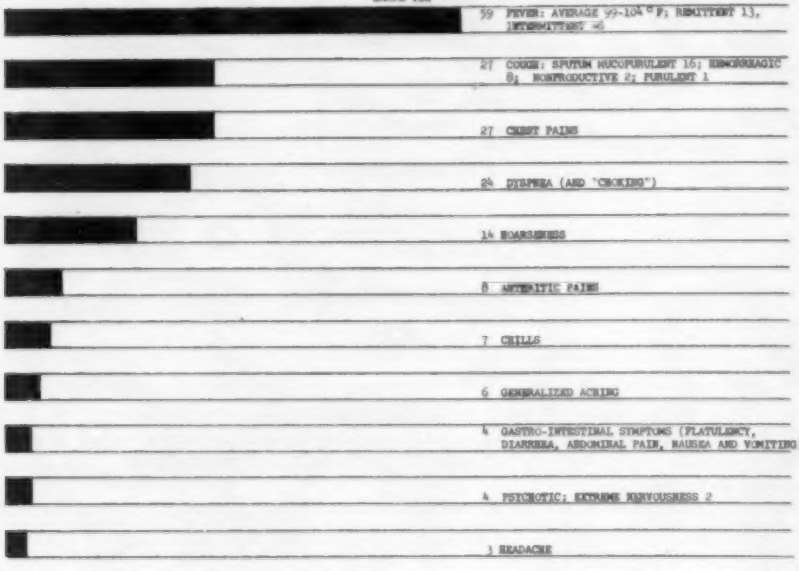
The 27 cases, consisting of 18 of my own and nine selected from the questionnaire (Graphs V and VI), studied in detail, present more specific data dealing with the various aspects of pulmonary brucellosis. The average age of the patients was 40 years and the ratio of males to females was 5:4. Forty per cent of the patients were associated with the cattle industry. The length of time before the diagnosis was made, which averaged 24 days in the acute, and 18 months in the chronic cases, suggests an unawareness of the diagnostic possibility of brucellosis on the part of the previous attendants. Certainly the acute cases were not observed for a sufficient time to guard against recurrence of their infection. The symptoms in order of frequency were fever, usually intermittent, weakness, muscular, neuritic and arthritic pain, loss of weight, cough, digestive disturbances, nervousness, mild psychoses, dyspnea, headache, pleurisy, enlarged nodes and pleuritic pains. The physical findings were markedly evident in the acute but not conclusive in the chronic cases. The chest x-ray findings in order of frequency were perihilar thickening, peribronchial infiltrations, nodular areas in the parenchyma, millet-seed calcifications, and infrequently, pneumonic consolidations, pneumonitis, pleural adhesions and atelectatic areas. There were no definitive findings in the routine blood examination except a slight leukopenia and relative lymphocytosis in the acute cases. The blood culture was positive in only three patients. The brucellergin test was positive in the 20 in whom the test was made. The agglutination reaction was positive in all. The mean Modified Foshay opsonocytophagic test was 30, indicating a moderately low level and a lack of balance between infection and immunity. All five

GRAPHIC CHART SHOWING SUMMARY OF X-RAY FINDINGS OF 27 CASES OF PULMONARY BRUCELLOSIS, 9 FROM UNITED STATES VETERANS HOSPITALS AND 18 OF MY OWN.
GRAPH VI



acute cases seemingly recovered, at least of their one attack of brucellosis; the chronic cases revealed a more dismal picture of whom eight were successfully treated, one with aureomycin and seven with a cobalt, copper manganese combination. The daily dosage of cobalt, copper and manganese was 0.4 mg., 0.15 mg., and 0.5 mg., per kilogram of body weight. This indicates that a patient weighing 70 kilogram would receive cobalt carbonate ($2CoCO_3 \cdot 3CO(OH)_2$) 112 mg., cupric sulphate USP XI ($CuSO_4 \cdot 5H_2O$) 42 mg., and manganese carbonate ($MnCO_2$) 70 mg. The daily requirement should be divided into three doses per day. A convenient method to use is to have the cobalt carbonate, cupric sulphate USP XI and the manganese carbonate made up in No. 3 capsules, each containing cobalt carbonate 37 mg., cupric sulphate USP XI 14 mg., and manganese carbonate 23 mg., in each capsule. One capsule should be given three times a day after meals for a period of six weeks followed by a rest period of three weeks and then resumed and continued in this alternate manner throughout the first year. If small doses are indicated in patients with lesser weight one or two capsules may be prescribed in such patients. A routine blood count and Modified Foshay index should be made once each month during this year of treatment. There is no objection to continuing the treatment for longer than one year unless some untoward side effect is noted, however, I have never observed any such reactions. If the clinical progress has not been satisfactory the treatment should be continued throughout the second year as it is to be remembered that patients might relapse after varying periods of time. After termination of the treatment patients are advised to return every three months for an additional two years.

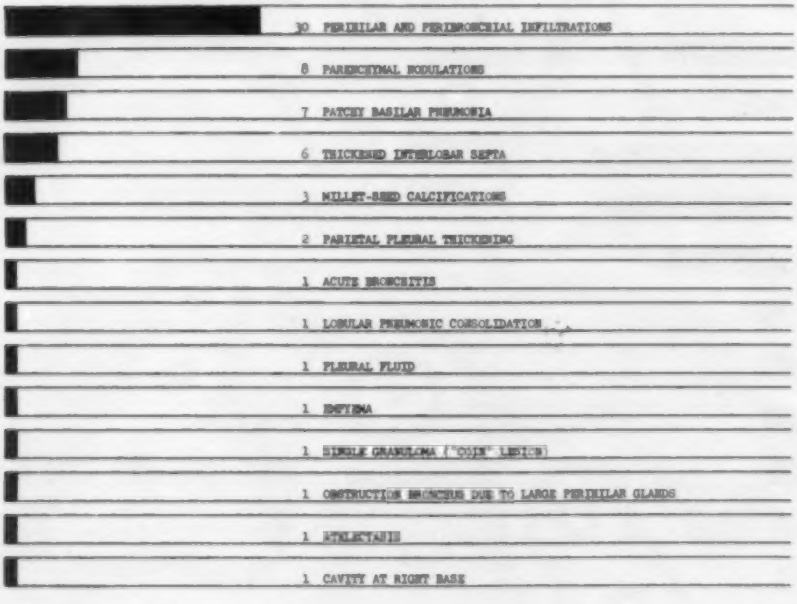
GRAPHIC CHART SHOWING RELATIVE FREQUENCY OF THE LEADING SYMPTOMS IN ALL CASES
GRAPH VII



Discussion

Since blood cultures for Brucella are not readily available in a large proportion of the cases of chronic brucellosis, we must revaluate the specific importance of additional laboratory tests when blood cultural studies are not obtainable. The present-day tendency to rely on a few blood cultures, or in conjunction with the agglutination test in chronic brucellosis, may lead to frequent diagnostic failures. It is true the agglutination reaction is usually positive in cases with positive blood cultures, but this relationship is not necessarily true; in chronic brucellosis, especially the abortus type, the finding of a positive blood-agglutination reaction in a significant titer is the exception rather than the rule. Its persistent absence or presence in a low titer has been reported repeatedly in both acute and chronic cases with positive blood cultures, however, it is a valuable adjunct whenever a positive blood culture is not obtained. It is obvious we cannot rely entirely on either the blood culture or the blood-agglutination reaction singly, because one or both tests may be negative in both acute and chronic brucellosis. Especially is the latter statement true, if the brucellar infection is well localized within the body of the patient. The agglutinins may be fleeting and bear no relationship to the activity of the disease. It is also an erroneous concept that lessening of the blood-agglutination titer indicates a favorable prognosis. The intradermal brucellergin test should be deferred until after the agglutination and opsonocytophagic tests have been concluded; otherwise, agglutinins

GRAPHIC CHART OF X-RAY FINDINGS SHOWING RELATIVE PROPORTIONS OF VARIOUS FINDINGS IN 59 CASES
GRAPH VIII



and opsonins may be stimulated and the value of the test of little importance. Many physicians use the skin test as the sole diagnostic procedure. The significance of the test is comparable, generally speaking, to that of the intradermal tuberculin test, and if positive, indicates usually that the patient has been infected with Brucella at some previous time. A positive intradermal brucellergin reaction does not determine the present status of the brucellar infection. I am inclined toward the assumption a positive intradermal reaction might denote the presence of viable Brucella organisms localized within the body, although not implying the presence of active disease. A positive skin reaction assumes specific significance as a diagnostic procedure when the opsonocytophagic test, as well, demonstrates the presence of opsonins for the organism. The relationship does not always coexist, since either or both skin and the opsonic tests may be negative in the presence of latent or active infection. A positive intradermal reaction, whatever the degree—low or high, when associated with the presence of specific opsonins, especially of low titers, indicates the presence of an infection with Brucella. The diagnosis of active brucellosis depends upon the skill and judgment of the physicians and repeated laboratory and clinical observations over a period of months. It is in this way a diagnosis may be made. We are not dealing with a disease similar to typhoid and typhus fevers, but more like tuberculosis. We would certainly not discharge a patient with tuberculosis after three weeks treatment with antibiotic therapy. It is well known that acute brucellosis frequently relapses and may persist as a low-grade infection for months or years, or may remain localized for years, subsequently assuming an active status as a really severe disease process. It is my opinion that in the cases with pulmonary involvement localization may occur in the hilar nodes and the small nodularities in the pulmonary parenchyma observed in the x-ray films of the chests of my cases.

CONCLUSIONS

A survey of 41 cases of pulmonary brucellosis, furnished me by 13 of 187 chest specialists has been reviewed. Nine cases were selected from the 41, and combined with 18 of my own, and were subjected to a detailed analysis. Involvement of the lungs by brucellosis has received scant attention in the literature, and the fact that only 13 of 187 physicians had seen such localization, suggests a widespread unawareness of pulmonary brucellosis, especially the chronic type, in the minds of physicians generally. The disease has a tendency to develop latency or a chronic, subclinical infection; therefore, such patients should be observed and checked for many months after they have seemingly recovered. The relative value of the various diagnostic tests has been stated. The treatment of the acute cases with antibiotics is good from an immediate standpoint; how many may have relapsed subsequently we do not know nor wish to hazard a guess. The chronic cases constitute a real therapeutic problem as therapy is very unsatisfactory. The seven cases treated with a cobalt, copper and manganese combination with apparent recovery were

given this on an empirical basis. They attained good health, which was maintained for many months of subsequent observation. It is impossible for me to state at this time any reasonable and scientific explanation for the beneficial or curative effects of this mode of therapy. No claim is made, whatsoever, in regard to its specificity. My main object is to suggest its trial on an experimental basis by other physicians in order to determine its unworthiness or worth.

I wish to thank Doctors Oren A. Beatty, Louisville, Kentucky, J. L. Alexander, Savannah, Georgia, Daniel N. Pickar, Veterans Hospital. Louisville, Kentucky, Frank W. Pickell, Baton Rouge, Louisiana, C. W. Strickler, Jr., Atlanta, Georgia and Roy A. Wolford, Acting Chief Medical Director, Veterans Administration, Washington, D. C., for permission to analyze the charts in the Veterans Administration Hospitals in Houston, Texas and Louisville, Kentucky, and the 187 physicians who answered my questionnaire.

CONCLUSIONES

Se ha revisado una investigación de 41 casos de brucelosis pulmonar que me proporcionaron 13 de 187 especialistas de tórax. Se seleccionaron 9 casos de los 41 y junto con 18 míos fueron sujetos a análisis detallado. El compromiso de los pulmones en la brucelosis ha recibido poca atención en la literatura y el hecho de que sólo 13 de 187 médicos habían observado esta localización, sugiere un amplio desconocimiento de la brucelosis pulmonar, especialmente del tipo crónico, en la mente de los médicos por lo general. La enfermedad tiene una tendencia a hacerse latente o en la forma de una infección crónica subclínica; por lo tanto, tales pacientes deben ser observados e inspeccionados por muchos meses después de que parezcan haberse aliviado.

El valor relativo de las varias pruebas diagnóstico se ha indicado.

El tratamiento de los casos agudos con antibióticos es bueno desde un punto de vista inmediato. Cuántos habrán recaído posteriormente, no lo sabemos ni deseamos arriesgar un juicio. Los casos crónicos constituyen un verdadero problema terapéutico, ya que la terapia es muy poco satisfactoria. Los siete casos tratados con una combinación de cobalto, cobre y manganeso con alivio aparente, lo fueron con bases empíricas.

Lograron buena salud, que les fué mantenida por muchos meses de observación subsecuente. Es imposible para mí establecer una explicación científica razonable para los efectos benéficos o curativos de esta modalidad terapéutica. No se ha proclamado su especificidad. Mi objetivo principal es sugerir su ensayo con bases experimentales por otros médicos para determinar su falta o su positivo valor.

RESUME

L'auteur rapporte une étude de 41 cas de brucellose rassemblés par 13 des 187 spécialistes des affections pulmonaires. 9 cas furent choisis parmi ces 41 et associés à 18 cas personnels de l'auteur, et soumis à une analyse détaillée. L'atteinte des poumons par la brucellose n'a que faiblement retenu l'attention dans la littérature; le fait que treize seulement des 187 médecins aient vu une telle localisation permet de penser qu'il y a dans l'ensemble une grande méconnaissance de la brucellose pulmonaire (particulièrement du type chronique). L'affection a tendance à constituer une

infection infraclinique latente ou chronique: c'est pourquoi de tels malades devraient être observés et suivis pendant de nombreux mois après leur guérison apparente. L'auteur a constaté la valeur relative des différents tests de diagnostic. Le traitement par antibiotiques dans les cas aigus est une bonne chose dans l'immédiat. Mais l'auteur ne sait pas le nombre de malades qui en ont tiré un bénéfice réel, et ne veut pas hasarder d'hypothèse. Les cas chroniques constituent un réel problème thérapeutique car le traitement est très décevant. Les nombreux cas traités au cobalt, avec une combinaison de cuivre et manganèse, suivis de guérison apparente, furent traités ainsi sur une base empirique. On obtint une guérison qui se maintint après plusieurs mois d'observation ininterrompue. Il est impossible à l'auteur de donner pour le moment aucune explication scientifique ou logique des effets bénéfiques ou curatifs de ce procédé de traitement. L'auteur ne considère pas qu'elle doive être tenue pour spécifique. Son objet principal est de suggérer que les autres médecins fassent cet essai sur une base expérimentale, pour déterminer ou infirmer son efficacité.

SCHLUSSFOLGERUNGEN

Es wurde ein Überblick über 41 Fälle von Lungen-Brucellose gegeben, die mir durch 13 von 187 Lungen-Spezialisten zur Verfügung gestellt wurden. 9 dieser 41 Fälle wurden mit 18 meiner eigenen zusammengestellt und einer eingehenden Besprechung unterzogen. Der Befall der Lunge mit Brucellose hat bisher wenig Beachtung in der Literatur gefunden, und die Tatsache, dass nur 13 von 187 Ärzten diese Art der Lokalisation gesehen hatten, lässt darauf schliessen, dass besonders die chronische Lungen-Brucellose von den wenigsten Ärzten erkannt wird. Die Krankheit verläuft latent oder unter dem Bilde einer chronischen, subklinischen Infektion. Darum sollten scheinbar geheilte Patienten noch über Monate hinaus laufend beobachtet und kontrolliert werden. Der relative Wert der verschiedenartigen diagnostischen Teste wurde bereits erwähnt. Vom augenblicklichen Standpunkt erscheint die Behandlung der akuten Fälle mit Antibiotika zweckmässig zu sein; jedoch kennt man weder die Zahl der späteren Rückfälle noch ist eine Abschätzung derselben möglich. Chronische Fälle stellen ein eigentliches therapeutisches Problem dar, da die Therapie dieser Fälle sehr unbefriedigend ist. 7 mit einer Kombination von Kobalt, Kupfer und Mangen mit scheinbarem Heilerfolg behandelte Patienten erhielten diese Therapie auf empirischer Basis. Bei ihnen wurde ein guter Gesundheitszustand erreicht, der auch während viele Monate laufenden Nachbeobachtung standhielt. Es ist mir unmöglich, schon jetzt eine einwandfrei wissenschaftliche Erklärung der Heilwirkung dieser Form der Therapie zu geben. Immerhin wird auf die Spezifität dieser Behandlungsform kein gültiger Anspruch erhoben. Hauptziel meiner Ausführungen ist jedenfalls, ihre Erprobung auf wissenschaftlicher Basis durch andere Ärzte anzuregen, um den Nachweis über ihren Wert oder Unwert zu erbringen.

Enzyme Therapy by Intramuscular Route in Chest Diseases

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Among the pathognomonic signs of bronchial asthma, chronic bronchitis and bronchiectasis is an accumulation of tenacious, inspissated mucus which becomes adherent to the tracheobronchial tree. This "gunk" may aggravate and create the edema of the bronchial mucosa, and contractions of the smooth muscle bundles with resulting bronchospasm, and even emphysema. The mucus, which becomes glairy and tenacious and which obstructs the bronchial lumen, produces a thickened basement membrane persisting in some patients for periods of many months to years, causing respiratory and social embarrassment. Many therapeutic agents and methods have been employed with varying degrees of success and efficiency[1] but none has satisfactorily removed these accumulations.

Enzymes have long been used in the laboratory to liquefy thick heavy sputum by direct lytic action. To investigate *in vivo* application, Limber et al[2] administered an aerosol of the enzyme trypsin to animals without untoward effect and therapy proceeded to clinical studies. Aerosolized solutions of trypsin were shown to be effective in loosening, thereby facilitating the raising of thick mucus, particularly from the upper part of the tracheobronchial tree. In their work with tuberculous patients, they concluded that the liquefying action was due to lysis of the mucus and also to stimulation of the cells of the mucous membrane lining the respiratory tract.

Unger and Unger[3] reported that aerosolized trypsin was effective in clearing the upper part of the respiratory tract in bronchiectasis, acute atelectasis, and bronchial asthma with infection, but the results in chronic bronchial asthma and emphysema were not as favorable. Our personal experience with aerosol trypsin was similar, but it was found that inhalation therapy was not tolerated by several patients because of the irritation to the mucous membrane. The findings of Farber et al[4] showed alteration of the epithelial cells of the trachea when trypsin solution was inhaled as an aerosol.

Rationale

When trypsin was given parenterally to patients with traumatic and varicose ulcers, a subsequent thinning of the heavy secretions was seen, followed finally by healing.[5, 6] It was therefore rationalized that if trypsin need not come into direct contact with an involved area in ulcers to produce an effective result, it might not have to make such a contact with thickened mucus in the respiratory tract in order to bring about either a

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mobilization or a liquefication of inspissated, glairy plugs. To investigate this premise in patients with such respiratory accumulations, trypsin was given by the intramuscular route to determine what value, if any, might be derived in cases of bronchial asthma, chronic bronchitis, and bronchiectasis.

Experimental Group

Thirty-seven patients were selected as a fairly representative group to study. Twelve were eliminated because of the findings of associated pathology not pertinent to the study. Of the remaining 25, three had chronic bronchial asthma, 10 chronic bronchitis with asthma, and the balance intermittent bronchial asthma of long standing. There were 23 adults, 14 males and nine females ranging in age from 19 to 67, and one child, a boy aged nine. Most of the patients had had asthma for seven years or longer. Age and the duration of their diseases are listed in Chart 1. On radiological examination, the patients showed varying degrees of localized or generalized emphysema, increases in the width and density of hilar shadows, and increases in the bronchovascular markings with streak-like shadows particularly in both bases. In 10, a honeycomb pattern with finger-like dense projections extending from the roots of the lung and with irregular areas of radiolucency, was felt to be evidence of bronchiectasis, although bronchoscopic examinations, were not made to confirm the diagnosis. The clinical findings of asthma and the x-ray findings in the lungs were of similar pattern in the 25 selected patients, but differed only in degree of pathology.

Methods and Materials

Complete blood counts, urinalyses, and nutritional blood assays were carried out in every patient before and after treatment. In addition, each patient was examined radiologically with postero-anterior and lateral films of the chest and the sinuses before and after treatment. Nine showing the greatest x-ray changes were filmed a third time, one to three months after enzyme therapy had been completed. The complete blood counts, urinalyses, and nutritional blood assay studies, although revealing, were not pertinent to the purpose of this paper, and are being discussed elsewhere.

Treatment

Each patient received injections in the buttocks of a preparation containing 5 mg. of trypsin per ml. of sesame oil according to the following formula for adults:

A first injection of 0.5 ml., and in the absence of side effects, one ml. (5.0 mg.) daily for five to seven days, then one ml. every second or third day for two weeks, and finally an injection one week later.

Children received 0.25 ml. for the trial dose, followed in 24 hours by 0.5 ml. (2.5 mg.) daily for five days, thence 0.5 ml. weekly for two weeks.

Seven patients were given a second course of treatment, and five a third course.

Side Effects

In no case was there a reaction to the first injection. Of the 25, one (Case 19) was unable to fully tolerate the enzyme, and by the third injection of her second course she reported severe pain in the hips, a diffuse rash about the pelvic girdle, and an exacerbation of her asthmatic syndrome. Several others complained of extreme pain at the site of injection, but were able to continue with therapy. The most unusual side effect was the development in several patients of a fine maculopapular rash about the entire pelvic girdle. Treatment, however, did not have to be interrupted beyond a few days, when the course was then completed. One complained of dizziness and light-headedness, but was still able to complete the treatments.

Interpretation of the Study

The subjective changes are included in Chart I. All found it much easier to raise the thick sputum within one to three days after starting trypsin. Every one reported feeling better after the first course of injections. The duration of improvement following a course of treatment varied from patient to patient. In some, pretreatment symptoms did not return in four to six months; in others, symptoms began to recur within 10 days to two weeks. A second course was given to seven with six responding as well the second time. The remaining patient reported an exacerbation of asthma on the third day of the second course and therefore trypsin was withdrawn. The five who received a third course responded well. One received 24 injections over a period of three months, during which time his asthma remained under adequate control.

Chart II shows the x-ray findings before and after treatment. The reports on the paranasal sinuses are not included because there were no consistent changes between the pre- and post-treatment examinations, although there was evidence of abnormality and pathology in every patient studied.

Evaluation of the results was made from the changes apparent in the post-treatment chest films when compared with the pre-treatment films.

Of the 25 cases, 13 showed marked improvement, nine, slight to moderate improvement, and three no change. The most frequent observation in the greatly improved patients was a marked decrease in the streak-like density. This was seen particularly in those cases where the finger-like projections and irregular areas of radiolucency were felt to be of bronchiectatic origin. Many showed definite decrease in the width of the bronchi. In none was there improvement in the emphysema.

Nine of the 13 who showed marked improvement were examined a third time some weeks after completion of therapy. Three showed the same degree and extent of increased bronchovascular markings as in the pre-treatment x-ray films, one had continuing improvement almost to normal chest findings, and the other five showed about the same improvement as in their first post-treatment examinations.

CHART I

Patient Age, Sex	Diagnosis	Treatment	Subjective Pretreatment	Subjective Changes	Subjective Side Effects
1. A.D. 57, F	Chronic bronchial asthma. Old chr. tuberculosis, 37 years	5 inj. daily, 3 inj. next wk., 1 a wk. later	Thick tenacious mucus. Large glandular swellings at neck and axillae present 30 years	Began raising voluminous gunk after third day. Swellings disappeared	Itch and lumps at inj. sites. Rash at neck and pelvic girdle
2. P.P. 20, F	Severe intermittent asthma, 8 years	5 daily, 3 in next week	Breathing with difficulty	Felt progressively better starting second day when she began to raise freely	None
3. E.S. 44, F	Asthma, chronic bronchitis for 9 years	6 daily, 2 in next week	Raising poorly	By 3rd day, pt. said feeling better, lighter. Improvement continued over course	Pain at pelvic girdle. Sore hips
4. C.F. 66, M	Bronchial asthma for many years	6 daily, 3 in next week	Has received allergy treatment for 18 years. Has had polyps removed from nose every 2 months for 16 years	Nose clear, breathing more easily, no polyps removed	Severe rash and pain in pelvic girdle
5. C.C. 31, M	Bronchial asthma for a year and a half	Twice daily for 4 days, 3 in next week	Hospitalized repeatedly for severe attacks. Has been taking 100 mg. cortisone daily for 15 months	Cortisone withdrawn abruptly. After 4 days began to raise tremendous quantities thick green sputum which thinned and turned yellow on subsequent days	None
6. P.K. 19, M	Bronchial asthma and hay fever 13 years	5 daily and 3 per week for 3 weeks	Difficulty breathing, congestion in chest	Raised large amount of sputum, felt well and lost all sense of congestion in his chest	None
7. L.C. 26, M	Asthma for 18 years	4 daily and 1 weekly or biweekly for 7 inj.	Has tried many physicians and many climates with no relief	Profuse raising dwindling to least amount he can remember. Says he feels better than he can remember	None

(*Continued on next page*)

CHART I—Continued

Patient Age, Sex	Diagnosis	Treatment	Pretreatment	Subjective Changes	Side Effects
8. E.W. 53, M	Severe bronchitis and asthma 35 years	6 daily and 7 over three weeks	Condition started in World War I	Is raising more freely, breathing easier and says he feels better	None
9. P.D. 40, M	Bronchial asthma for 27 years	4 daily, 3 in next week, 1 a week later	Severe chronic bronchial asthma with cor pulmonale	Began to raise freely by 3rd day, felt better on 4th. By end of treatment says he "feels good"	Sore and itchy buttocks. A fine rash
10. S.A. 64, F	Chr. bronchitis for 40 years. Asthma 6 months	4 daily, 3 in next two weeks, 1 a week later	Marked tightness in chest	Asthma completely disappeared. Feels much better	None
11. H.F. 35, M	Bronchial asthma and hay fever for 17 years	4 daily and 3 in a week	Severe asthma with difficulty breathing for several weeks	Began raising thick sputum 2nd day which thinned and diminished by 4th day. Acute episode cleared in a week	Markedly swollen hips
12. E.E. 38, M	Bronchial asthma and bronchitis 5 years	8 daily	History of thoracoplasty. Severe episodes of bronchitis and asthma	Progressively better after 2nd day when large amounts of yellow sputum began to raise	None
13. O.S. 67, F	Severe bronchitis 30 years. Asthma 7 years	5 daily, 3 in next week	Breathing with difficulty	Raising better by 4th day. Much better by end of treatment	Sore hips. Rash on both hips
14. C.N. 45, M	Bronchitis many years. Asthma 1 year	7 daily	Severe episodes of bronchial asthma and status asthmaticus	Began to raise on 3rd day. Reported sleeping much better than in many months	None
15. M.G. 9, M	Bronchial asthma and bronchitis 8 years	5 daily	Coughing and choking	By fourth day, mucus coming up freely. Very much better	None
16. D.C. 64, F	Chr. bronchitis 10 years. Severe bronchial asthma 5 months	4 daily	Coughing, choking, breathing with difficulty	Relief of asthma in 4 days	None

17. M.C.	25, F	Asthma 9 years	7 daily, 3 in next week	Hospitalized many times. Treated in many clinics and by numerous physicians	After a week, remarkably improved and raising freely	Pain in both buttocks, hips, and groin
18. N.S.	39, F	Severe bronchial asthma, 26 years	7 daily	Severe, intractable bronchial asthma and status asthmaticus	Asthma cleared and raised freely. On second course 2 months later reported asthma exacerbated by injections	Generalized rash on both buttocks, severe pain in pelvic girdle
19. E.H.	52, M	Bronchial asthma for 38 years	24 inj. over 12 weeks	Having a great deal of difficulty breathing and raising for years	Raising much easier. Patient feels there has been definite progress	None
20. H.L.	51, M	Bronchial asthma, bronchitis, hay fever for 30 yrs.	8 daily and 1 a week for 3 weeks	Large amounts of greenish-yellow sputum. Tightness in chest	Raising more easily and felt better by third day. States he feels well at end of course	None
21. P.P.	60, M	Bronchiectasis, hay fever from childhood. Asthma 1 year	5 daily, 3 next week, 2 a week for 2 weeks	Has had a very difficult time raising	Under treatment, patient raised easier and reported fewer attacks. Feels much better	None
22. P.T.	65, M	Bronchial asthma, status asthmaticus	8 daily and 3 in next week	Has been hospitalized several times with status asthmaticus. Unable to raise during episodes	Began to raise on 4th day and has been free of asthma since the 1st week	None
23. I.R.	46, F	Bronchial asthma 23 years	4 daily, 3 a week for 2 weeks	Has had all kinds of treatment with no prolonged relief	Began to feel better on 6th visit and has had no trouble since	None
24. M.T.	26, M	Severe bronchial asthma for 8 yrs.	5 daily, and 1 4 days later	Dry hard cough	States he can do more work with less effort than at any time in the last 4 years	None
25. C.L.	35, M	Bronchial asthma 13 years	5 daily, 3 second week, 2 at 1-week intervals	Severe intermittent episodes of coughing and wheezing	Raising facilitated, coughing diminished. Breathing easily	None

CHART II
X-RAY OBSERVATIONS

Patient	Pretreatment	Time Interval	Comparison	Time Interval	Follow-up
1.	Extensive calcification and numerous fibrous strands. Extremely hyperaerated and emphysematous. B-V markings extremely exaggerated. Healed pulmonary tuberculosis	19 days	No change in fibrosis, emphysema and calcification. Bronchovascular markings not nearly so prominent. On measurement at left base reduced from 5 or 6 mm. to half		
2.	Moderately hyperaerated with moderately increased bronchovascular markings	8 days	No essential change		
3.	Hilar regions increased in width and density. B-V markings extremely prominent in bases	10 days	No appreciable change		
4.	Markedly hyperaerated and emphysematous. Hilar regions markedly increased (2 to 3x normal). B-V markings very prominent throughout. All changes particularly marked on the right	11 days	Emphysema unchanged. Slight decrease in width of right hilar region		
5.	Extremely hyperaerated and emphysematous. Hilar region markedly increased, particularly on rt., and the B-V markings throughout are extremely prominent	12 days	Emphysema unchanged. Improvement in density and extent of B-V markings on rt. A slight but definitely greater aeration of lung at rt. hilus		
6.	Moderately hyperaerated and emphysematous. Hilar regions increased in width and density. B-V markings are prominent, particularly in lower half of both lung fields	7 days	Definite improvement in density of markings. Decrease in size of hilar region		

7.	Hilar regions markedly increased in width and density. B-V markings extremely prominent, especially through mid-lung. Moderately hyperaerated lungs	24 days	Marked improvement in density of B-V markings. The left lung field, though emphysematous, is clear	4½ months	Still greater improvement. Only slight emphysema and slightly increased B-V markings remain
8.	Hilar regions increased in width and density. B-V markings extremely prominent, particularly in bases. At rt. base suggestive of bronchiectasis	18 days	No evidence of change		
9.	Extremely hyperaerated and emphysematous. B-V markings extremely prominent, especially in left base	12 days	Same emphysema but a slight but definite decrease in B-V markings		
10.	Linear density (segmental) on right having appearance of atelectasis. Hilar regions increased in density and width. Bronchovascular markings extremely prominent. Left lung clear but emphysematous	28 days	A definite decrease in width of hilar region. Definite decrease in density and extent of B-V markings. No change in atelectasis or in emphysema	4½ months	Densities returning toward original x-ray, but there is still improvement
11.	The lungs are generally hyperaerated and emphysematous. B-V marking in lower half both lungs extremely prominent	14 days	No evidence of change		
12.	Thoracoplasty of rt. rib cage. Dense pulmonary fibrosis and adhesions. Rest of lungs are hyperaerated and emphysematous. Hilar regions increased to two more times normal width, B-V markings extremely prominent in both bases	9 days	Bronchovascular markings show a definite decrease in density		

(*Continued on next page*)

CHART II—Continued

Patient	Pretreatment	Time Interval	Comparison	Time Interval	Follow-up
13.	Lungs hyperaerated and emphysematous throughout. B-V markings extremely prominent, particularly in lower two-thirds	10 days	No change in emphysema. B-V markings not nearly as prominent, especially in left base		
14.	Lungs hyperaerated and emphysematous throughout. Hilar region increased in density and width. B-V markings moderately thickened, particularly in right lung field	7 days	Marked lessening of B-V density, particularly in right base	4 months	Return to original picture
15.	Lungs hyperaerated and emphysematous. B-V markings extremely prominent throughout	9 days	Marked decrease in B-V markings, particularly right base and right hilus		
16.	Left base to 3rd rib occupied by linear and mottled densities on right and markedly thickened and prominent B-V markings	10 days	Dramatic improvement in all densities	3½ months	Left base practically in normal limits showing no further improvement. Rest of lungs emphysematous but clear
17.	Lungs throughout are extremely hyperaerated and emphysematous. Hilar regions markedly increased in width and density. Extremely exaggerated B-V markings, especially on left	14 days	A definite change in the B-V markings on left—not nearly so prominent or dense. No change on right	4½ months	Return to same degree of markings as in first examination
18.	Marked emphysema and hyperaeration. B-V markings in whole field, particularly upper, markedly thickened	10 days	Reduction in B-V markings	5 months	Return to original findings. Could not tolerate 2nd course

19.	Extremely hyperaerated and emphysematous. Hilar regions increased in width and density. B-V markings extremely prominent through lower ⅔ of both lungs	14 days	Marked improvement in density. Except for emphysema, markings almost normal range	1½ months	(continued trypsin.) B-V markings slightly more prominent than last examination
20.	Extremely hyperaerated and emphysematous. B-V markings extremely prominent throughout	8 days	No essential change	3 months	Still no change
21.	Extreme emphysema and hyperaeration. Hilar regions increased in width and density particularly on right. B-V markings increased markedly throughout. Suggestive of bronchiectasis	7 days	Slight decrease in B-V markings at right base and slight decrease at left hilus		
22.	Extreme emphysema through both lungs, most marked on the left. B-V markings extremely prominent through both bases and at right base suggest extensive bronchiectasis	14 days	At right base B-V markings not nearly so prominent, also at lung fields marked diminution of density		
23.	Hyperaeration and emphysema. Prominent B-V markings	7 days	No change		
24.	Hyperaerated, particularly left base. B-V markings prominent, particularly through left lung field	9 days	Emphysema unchanged. A marked diminution of B-V markings on left. Right remains unchanged		
25.	Marked emphysema, peribronchial fibrosis and pansinusitis	10 days	Decrease in B-V markings in both bases, particularly marked on the right	3 months	Return of B-V markings almost to original examination

Discussion

The uniformity of response of these patients was striking. All had difficulty raising sputum before treatment, and all raised copiously and with ease after a few days of trypsin. Subsequently, in all, the volume of secretions was diminished and breathing was easier. All felt better after a course of injections, the effect appearing to last for a period of 10 days or more. There is some indication that the improvement can be maintained with continued injections at weekly intervals; however, with this limited series there is insufficient evidence to complete any conclusion. Second and third courses appear to be as effective as the first.

Radiologic examinations of the chest show bronchovascular markings due not only to the outline of the bronchus, but also to the accompanying blood vessels and lymphatics. However, in any type of bronchiectasis where the bronchus is filled with inspissated secretion the shadow is due almost entirely to the bronchus. Many radiologists assume that the streak-like markings and minute nodules in the lung fields, considered to be due to an interstitial pneumonitis as well as to thickening of the bronchial walls, are more or less irreversible. The shadows are thought to be due to destruction of elastic tissue by repeated inflammatory attacks. The bronchi are therefore widened permanently and filled with secretions which throw characteristic sac-like dense shadows. The improvement of markings in such dramatic fashion in half of the patients is assumed to be caused by the expulsion or absorption of thickened mucus or mucopurulent material. As the most favorable results were seen in patients suspected from radiologic evidence of having bronchiectasis, bronchographic examinations are planned to establish the diagnosis and will be reported later.

From a medical standpoint, the effect of intramuscular trypsin might well be attributed to the lysing of mucus and the freeing of heavy immobile deposits in the bronchi and bronchioles. The lytic action may be indirect and due to activation of major lytic forces within the body or to stimulation of local cells to secrete a lytic substance.

In addition to the action on sputum, however, the effect of trypsin on local circulation must be considered. Increased flow in minute vessels to cause reduction in local edema has been suggested as the mechanism of trypsin's reversal of inflammation. It is possible therefore that the decrease in bronchovascular markings is partly due to an increase in local blood and lymph flow in the involved area, with resultant decrease in inflammation and reduction in the size of distended small vessels surrounding fibrous tissue.

The changes in bronchovascular markings include both thickness and density. In one case, linear and mottled densities suggestive of extensive bronchiectasis or of partial atelectasis showed dramatic improvement in a period of 10 days with still further improvement over the ensuing three months. It is hardly conceivable that this form of therapy can produce a reversal of the fibrotic process, but it is possible that some of these markings represent pre-fibrotic changes which are actually reversible. Chronic

inflammatory changes of the bronchiolar mucous membrane and edema possibly are precursors of pulmonary fibrosis and emphysema, as such changes have been seen on histologic examination of the lungs of such patients. Trypsin has been reported to reverse inflammation and to reduce edema following trauma and peripheral vascular conditions, and may be acting similarly in these asthmatic patients.

Since this study was undertaken a year ago, a report by Golden[7] has appeared in which clinical results obtained from intramuscular trypsin were discussed. Eight acute asthmatics treated for one to three days with a single daily injection of 0.5 ml. (2.5 mg.) during an acute episode were reported to obtain relief from paroxysms. Fourteen of chronic bronchial asthma treated with three to 22 injections responded with thinning of secretions and lessening of cough and orthopnea. The improvement was slow over a period of five to 15 days with daily half-ml. injections containing 2.5 mg. of trypsin.

The physiologic changes seen in the 25 patients reported in this series are being studied in greater detail, particularly in regard to maximum breathing capacity and vital capacity. These findings and additional clinical follow-up will form the basis of a subsequent report.

SUMMARY AND CONCLUSIONS

Twenty-five asthmatic patients with chest pathology of long standing who were placed on intramuscular trypsin showed definite improvement in their physical condition, not only subjectively but also objectively by x-ray film studies.

Abnormal bronchovascular markings on x-ray film examination previously interpreted as irreversible have shown changes which may well require re-evaluation and re-interpretation of such findings.

The author wishes to express his appreciation to Dr. M. Reingold for taking and reading the x-ray films.

The study was made possible through the kind co-operation of Mr. William Swain of the Clinical Research Department, National Drug Company.

RESUMEN Y CONCLUSIONES

Veinticinco pacientes asmáticos con patología torácica de larga duración que fueron puestos bajo tratamiento con tripsina intramuscular mostraron mejoría definitiva de su condición física, no sólo subjetivamente sino también objetivamente en estudios radiográficos.

Las sombras bronchovasculares anormales mostradas en las radiografías previamente interpretadas como irreversibles han mostrado cambios que pueden hacer necesaria una re-evaluación y reinterpretación de tales hallazgos.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

25 asthmatische Kranke mit hartnäckigen Lungenerkrankungen zeigten unter intramuskulär verabreichtem Trypsin Besserung ihres körperlichen Allgemeinzustandes, die sowohl subjektiv als auch objektiv röntgenologisch nachweisbar war.

Abnorme bronchovaskuläre Befunde, die röntgenologisch nachweisbar waren und früher als irreversibel angesehen wurden, zeigten Veränderungen, die erneute Untersuchung und Interpretation solcher Fälle notwendig machen dürften.

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Does a Hemorrhagic Tendency Exist in Patients Under Isoniazid-Streptomycin Treatment?

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The communications concerning the action of isoniazid and its derivatives on the clotting and bleeding mechanism and on hemorrhagic tendency are so conflicting that it is difficult if not impossible to draw definite conclusions from the available literature. The first communications on the treatment of tuberculosis with hydrazine derivatives of isonicotinic acid do not mention any toxic effect on the blood clotting mechanism or on the capillary walls. The later reports on isoniazid and its derivatives mention the possibility of hemorrhages, particularly of hemoptysis,[1, 2, 3, 4, 5] and others, of cerebral purpura with or without hemorrhagic effusion or cerebral edema,[7, 8] of purpura with or without thrombocytopenia,[2, 5, 9] of increased menstrual flow,[3] of retinal hemorrhages,[5] of rectal bleeding and bloody joint effusions.[2] Other investigators have not found any increased bleeding tendency in such patients,[10, 11] or were able to find any abnormality in bleeding or clotting mechanism.[10]

Different mechanisms were considered responsible for the alleged bleeding tendency. Clotting and prothrombin time both were found increased by some,[1, 12] prothrombin time found normal by others,[17] clotting time was found increased, bleeding and prothrombin time being normal (cited by 13), again some found prothrombin time only slightly increased capillary fragility being considerably impaired.[14] Some authors found no effect on prothrombin, bleeding and clotting time as well as on platelets count and explain the bleeding tendency by increased capillary fragility due to the action of the drug.[5, 6, 15, 16]

The possibility of increased sensitivity of the organism caused by isoniazid was also considered as a factor contributing to the bleeding tendency.[5] It was suggested that the hypersensitization, caused by the disintegration of body substance of tubercle bacilli, may lead to toxic destruction of pulmonary tissue with subsequent hemoptysis.[1]

In view of such conflicting reports the present writer conducted study upon the action of isoniazid on hemorrhagic tendency in the patients receiving this treatment both from the clinical and the laboratory points of view.

Two hundred eighty-seven unselected patients with pulmonary tuberculosis, who received isoniazid in the period from April 1952 to September 30, 1954, were taken for the clinical study.

Only cases with pulmonary tuberculosis of reinfection type, in a few instances with concomitant extra-pulmonary tuberculosis manifestations, were studied. Cases of extra-pulmonary tuberculosis in the absence of pulmonary manifestations were omitted. All were receiving combined

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isoniazid-streptomycin treatment. (It has been stated that streptomycin does not affect the bleeding and clotting mechanism[17, 18]). Cases were eliminated from this study if para-aminosalicylic acid or any other salicylates were given concomitantly for a longer time. Cases were also eliminated in which isoniazid or para-aminosalicylic acid was given preceding the admission. As a rule, streptomycin was given 1 gm. twice a week (with very few exceptions where daily streptomycin was given) and isoniazid with average of 4 mg. per kilogram daily.

The duration of isoniazid-streptomycin ranged from three months (in a few instances) to as long as two years and five months, the average duration of time being ten months. (In many cases the treatment has not yet been completed.)

Every patient was given thorough investigation as to the past history of any bleeding episodes and the charts, the laboratory reports as well as detailed daily nurses' notes gave a complete record of every change in the patient's condition with special attention to the amount and appearance of sputum. Not only hemoptysis, but also minimal streakings, were noted.

For the laboratory study 57 unselected patients were taken in order of their admission to the hospital and 42 were completed. In the remaining, two died before the completion of the study, three were transferred to other hospitals, in two the diagnosis of tuberculosis was reversed, in two isoniazid was substituted by other drugs and six left against advice. The tests were done before the beginning of the treatment, 5, 10 and 15 weeks after, the average dose of isoniazid being 4 mg. per kilo., and streptomycin, 1 gm. twice a week, as in the clinical study.

The following tests were done: Clotting time, bleeding time, prothrombin time, platelets count and in 24 patients capillary fragility test. The increase or reduction in figures was expressed in percentage of the initial (pretreatment) value, which was deliberately designated as 100 per cent for the given individual. This, in the writer's opinion, gave individual evaluation of every deviation from the pretreatment value which followed the treatment.

Clotting time was determined using Sabraze's capillary tube method, for determination of bleeding time the Duke's method was used, for prothrombin time—Quick's technique, the value being expressed in seconds. Platelets were counted by direct method, using the Rees-Ecker diluting fluid.

Capillary fragility test (Rumpel-Leede sign) was done according to Hess: After the blood pressure cuff had been kept inflated for 15 minutes in the usual position on the arm midway between systolic and diastolic pressure, the petechiae were counted under the magnifying glass in a 2.5 cm. diameter circle on the flexor surface of the forearm. Appearance of new petechiae from one to 10 was considered normal, from 11 to 20—as moderately increased capillary fragility and over 21—was interpreted as a sign of highly increased capillary fragility.

Unfortunately, the fragility test was not performed before starting the treatment and was done only once during treatment, 15 weeks from the beginning of chemotherapy, and only on 24 patients.

Among 287 patients on isoniazid-streptomycin none developed purpura, no increased menstrual flow was noted, no unexplainable rectal bleeding occurred and in six cases microhematuria was noted. In two of these cases initial value percentage and urine cultures showed the presence of tuberculosis, in two others urine was positive for tubercle bacilli and initial value percentage showed picture suspicious for tuberculosis and in two there was evidence of prostatitis and urethitis of unknown etiology. None of these hematurias could have been attributed to isoniazid. One developed retinal hemorrhage. Since she was 76 years old, diabetic and hypertonic, it is believed there was sufficient reason to explain this hemorrhage without implicating isoniazid.

Table I gives the figures obtained:

TABLE I

Number of Patients	Number of Patients with History of Hemorrhage Prior to Initiation of treatment	Number of Patients Admitted with or Because of Hemorrhage	Number of Patients Who Developed Hemoptysis or Streaking While on Isoniazid-Streptomycin
287	59 (20.6 per cent)	33 (11.5 per cent)	23 (8 per cent)
(The total of first two groups is 92 patients or 32.1 per cent.)			

Table I shows that 8 per cent of all patients on combined isoniazid-streptomycin developed hemoptysis or streaking at least once and that 32.1 per cent had hemoptysis (some repeatedly) in the past or were admitted right after or during hemoptysis. The hemorrhagic tendency showed a decline since isoniazid-streptomycin was initiated, as can also be concluded from Table II.

TABLE II

Number of Patients with History of Hemoptysis or Admitted With or Because of Hemoptysis	Number of Patients of This Group Who Developed Hemoptysis While on Isoniazid-Streptomycin
92	15 (16.3 per cent)

All 92 patients included in Table II with history of hemoptysis or admitted because of hemoptysis were active cases, many of them being in a worse condition than during previous hemorrhagic episodes. Table II shows a diminishing bleeding tendency under the action of isoniazid-streptomycin treatment.

Table III shows how many patients with hemoptysis or streaking while on isoniazid-streptomycin hemorrhaged before initiation of treatment and how many had their first bleeding episode.

TABLE III

Total of Patients	Total of Hemoptysis	Hemorrhaged Before Initiation of Treatment	First Developed Hemoptysis While Under Treatment
287	23 (8 per cent of total)	15 (5.2 per cent of total)	8 (2.8 per cent of total)

Out of the eight patients who developed hemoptysis or streaking for the first time while on isoniazid-streptomycin regimen, one bled after a drinking bout, another streaked after having returned from being absent with-

out leave, in three cases there was far advanced silico-tuberculosis, which failed to respond to chemotherapy. (One of them died of hemoptysis.) There is no reason to assume that in either of these cases isoniazid-streptomycin might have been the causative factor of hemoptysis—in fact, there was sufficient reason to explain the cause by the patient's abnormal activity or by the nature of the disease. In the other three cases it is impossible to establish the causal relationship between hemoptysis and chemotherapy—it might as well be explained by the nature of the disease.

It is our impression that since the introduction of isoniazid the incidence of hemoptysis and streaking in tuberculous patients has markedly declined.

Eighty-nine patients underwent surgery while under isoniazid-streptomycin treatment, as shown in Table IV.

TABLE IV

Type of Surgery	Number of Patients	Number of Operations	Abnormal or Excessive Bleeding During Surgery	Per Cent	Abnormal or Excessive Bleeding in the Postoperative Period	Per Cent
Pulmonary resections of all kinds	36	38	1	2.63	1	2.63
Thoracoplasties (primary and secondary)	18	24			1	4.2
Pneumonolysis	28	32	1	3.1	4	12.5
Monaldi	2	2				
Other major surgical procedures	5	5				
TOTAL	89	101				

There was no increased bleeding tendency in the resection group except for one case which showed more bleeding during and after surgery; postoperative bleeding required re-exploration at which time no bleeding point was found. The surgeon considered it "as just a general capillary ooze." Since there is no explanation for this bleeding (blood clotting mechanism was not determined in this patient before and during isoniazid treatment) one may speculate as to the effect of the drug in this particular case. In the thoracoplasty group the severe hemorrhage following surgery was due to bleeding from a blood vessel in the operative area and is explainable on that basis.

In the pneumonolysis group in one case the bleeding occurred from the adhesion during the procedure of severing it, but did not prevent the completion of surgery, in four cases from 100 to 400 ml. of blood tinged fluid was aspirated from the thoracic cavity following lysis. Such bleedings are usual in pneumonolysis and also happened before the introduction of isoniazid.

It seems to us that the incidence and severity of our operative and postoperative hemorrhages were within a normal range and we have no justification whatsoever to speak of an increased hemorrhagic tendency in isoniazid-streptomycin patients during and after surgery.

The results of laboratory studies showed a certain range of variation, but no definite trend or pattern, as can be seen from Table V.

TABLE V

Bleeding time was:
prolonged in 25,
unchanged in 5,
decreased in 12.
Average percentage of prolongation in bleeding time—2.8 per cent.

Clotting time:
prolonged in 27,
unchanged in 10,
decreased in 5.
Average percentage of prolongation in clotting time—13 per cent.

Prothrombin time:
prolonged in 17,
(diminished prothrombin activity)
unchanged in 7,
decreased (increased prothrombin activity) in 18.
Average decrease of prothrombin time (increase of prothrombin activity) 0.74 per cent.

Number of platelets:
increased in 23,
unchanged in 7,
diminished in 12.
Average increase in the number of platelets—9 per cent.

Capillary fragility:
normal in 19,
increased in 5,
(moderately in 3,
markedly in 2).

The final evaluation of laboratory tests was made at the end of the 15th week of isoniazid-streptomycin treatment.

Clotting time was prolonged on the average by 13 per cent of initial value. Assuming the normal range as determined by Sabraze's capillary method between three and seven minutes with an average of five minutes, 13 per cent increase of the average would represent 39 seconds. Such an increase is negligible from the clinical standpoint and must be considered within a range of normal physiological variations. Incidentally, the highest figure for clotting time in the entire group was six minutes and 30 seconds —still within normal limits.

The variations in bleeding and prothrombin time are so insignificant that they cannot be taken into consideration. As to the increase in number of platelets—9 per cent on the average—this should also be considered as a normal variation, physiological or purely incidental, depending on the counting technique.

Capillary fragility was increased in five out of 24 cases. Unfortunately, capillary fragility was not determined in these cases before starting drug treatment. However, the analysis of five cases with increased fragility shows that other than chemotherapeutic factors might have been implicated for the increased capillary fragility in at least two and, possibly, in three cases. Two were diabetics over 60 years of age with evidence of

arteriosclerosis. One could expect to find an increased capillary fragility in both of them. One was a man of 56 years, chronic alcoholic, with delirium tremens, polyneuritis and signs of cerebral sclerosis. Whether the increased capillary fragility was due to drugs or was a manifestation of the alcoholic condition—cannot be determined. Two others were in their 30's, one of them a chronic alcoholic, and the action of isoniazid might as well be considered as a possible causative agent of increased capillary fragility. However, this is not conclusive.

Discussion

The present study was carried out to determine whether there is an increased bleeding tendency under long term isoniazid-streptomycin and whether this treatment affects the clotting and bleeding mechanism. No increased bleeding tendency could be found during the clinical study. In fact, it appears that hemorrhagic accidents in patients on isoniazid-streptomycin showed an abrupt decline since the introduction of isoniazid. This could not be considered as a specific action of the chemotherapeutic agent on the blood clotting and bleeding mechanism—such action does not exist, as can be seen from our laboratory study—but merely represents a manifestation of a general improvement under the action of the drug. There was also no evidence of increased bleeding tendency during and after surgery in patients on isoniazid-streptomycin treatment and it is the writer's opinion that the fear of hemorrhage in tuberculous patients under such treatment during and after surgery is unjustified. The laboratory study shows variations within physiological range and the tests failed to provide any evidence of increased hemorrhagic tendency or of any definite trend. The capillary fragility was found to be normal in 79.2 per cent and only in 12.5 per cent there was no definite explanation for the increase in fragility by other, than chemotherapy, factors and the action of isoniazid might be considered as one possible factor. However, further studies should be done to confirm or deny the assumption of some European writers that capillary fragility is being affected by the action of isoniazid. So far, our clinical and laboratory study failed to provide any definite support for such an assumption as well as to prove the existence of an increased bleeding tendency in patients receiving isoniazid-streptomycin.

SUMMARY

1. Two hundred eighty-seven patients with pulmonary tuberculosis were studied in order to determine whether isoniazid-streptomycin increases the hemorrhagic tendency. Eight per cent of the patients developed hemoptysis or streaking, 5.2 per cent of these have also had hemoptic episodes before initiation of treatment, 2.8 per cent for the first time. Fifty-nine were admitted with history of hemoptysis and 33 admitted because of hemoptysis. Only 15 of the 92 (16.3 per cent) developed hemoptysis while under treatment and most of them in the first trimester of treatment. In the eight (2.8 per cent) who developed hemoptysis for the first time while under treatment, bleeding could have occurred due to the nature of the disease—all of them were far advanced cases, three with silico-tubercu-

losis — or explained by unusual activity, drinking, etc. — and not necessarily due to action of isoniazid. Apparently the drug definitely decreased the incidence of hemoptysis in tuberculous patients.

2. No other bleeding (renal, rectal etc.), attributable to chemotherapy, was noted during the study.

3. There was a normal incidence of operative and postoperative bleeding with one exception, where the mechanism was not determined.

4. Laboratory study of clotting, bleeding and prothrombin time and of platelets count before and during treatment showed a variation within physiological limits without any definite trend or pattern.

5. Capillary fragility was normal in 79.2 per cent and increased in 20.8 per cent. However, only in 12.5 per cent there was no definite explanation for the increase of fragility and in these cases chemotherapy could be considered as one of the possible factors. Further studies are suggested.

RESUMEN

1. Se estudiaron doscientos ochenta y siete enfermos de tuberculosis pulmonar para determinar si el uso de la isoniacida-estreptomicina aumentaba la tendencia hemorrágica.

Ocho por ciento de los enfermos presentaron hemoptisis o esputos estriados; 5.2 por ciento de estos habían tenido también hemoptisis antes de iniciarse el tratamiento; 2.8 por ciento la tuvieron por primera vez.

Cincuenta y nueve por ciento ingresaron con antecedentes de hemoptisis y 33 entraron por tener hemoptisis.

Sólo 15 de 92 (16.3 por ciento) presentaron hemoptisis mientras estaban en tratamiento y la mayoría en el primer trimestre de la cura. En los ocho que tuvieron hemoptisis (2.8 por ciento) por primera vez al estar en tratamiento, la hemorragia pudo ocurrir a causa de la enfermedad—todos eran casos avanzados, tres con silico-tuberculosis, o podrían explicarse por actividad inusitada—beber, etc., y no necesariamente a causa de la acción de la isoniacida. Aparentemente la droga definidamente disminuyó la frecuencia de las hemoptisis en los tuberculosos.

2. No se encontró otra forma de hemorragia (renal, rectal, etc.) atribuible a la quimioterapia durante este estudio.

3. Hubo una incidencia normal de hemorragia operatoria y postoperatoria, con una excepción en la que el mecanismo no se determinó.

4. Los estudios de laboratorio de la coagulación, sangrado y tiempo de protrombina así como la cuenta de plaquetas antes y durante el tratamiento mostró variaciones dentro de los límites fisiológicos sin ninguna tendencia definida.

5. La fragilidad capilar fué normal en 79.2 por ciento. Sin embargo, sólo en 12.5 por ciento no hubo explicación definida para el aumento de la fragilidad y estos la quimioterapia podría considerarse como uno de los factores posibles.

Se sugiere la necesidad de estudios ulteriores.

RESUME

1. L'auteur a suivi 287 malades atteints de tuberculose pulmonaire, afin de déterminer si le traitement par l'isoniazide-streptomycine accroit la tendance à l'hémorragie. 80% des malades firent des hémoptysies, parmi eux 5,2% avaient présenté des manifestations hémoptoïques avant l'institution du traitement, 2,8% pour la première fois. 59 malades avaient eu dans leur passé une hémoptysie et 33 ont été admis pour hémoptysie. 15 malades seulement sur les 92 (16,3%) firent des hémoptysies pendant qu'ils étaient traités et la plupart d'entre eux pendant le premier trimestre du traitement.

Sur les huit malades (2,8%) qui firent des hémoptysies pour la première fois pendant le traitement, on pouvait invoquer le caractère des lésions (tous étaient porteurs de formes graves, trois étaient atteints de silico-tuberculose) ou leur caractère exceptionnelement évolutif, plutôt que l'action de l'isoniazide. Apparemment le produit a une action nettement favorable sur la fréquence des hémoptysies chez les tuberculeux.

2. Aucune autre hémorragie (rénale, rectale, etc. . . .) attribuable à la chimiothérapie ne fut notée dans cette étude.

3. La fréquence des hémorragies opératoires et post-opératoires fut normale. Dans un seul cas l'hémorragie semble inexplicable.

4. L'étude des temps de coagulation et de saignement, le dosage de la prothrombine, et la numération des plaquettes avant et après traitement donnèrent des résultats qui restaient dans les limites physiologiques.

5. L'étude de la fragilité capillaire donna des valeurs normales dans 79,2% des cas et augmentée dans 20,8% des cas. Cependant dans 12,5%, on constata une augmentation de la fragilité capillaire que l'on ne pouvait expliquer de façon précise. On aurait pu alors l'attribuer à la chimiothérapie.

L'auteur propose que soient poursuivies des études ultérieures.

ZUSAMMENFASSUNG

1. Es wurden 287 Kranke mit Lungentuberkulose untersucht in der Absicht, zu bestimmen, ob INH-Streptomycin die Neigung zu Blutungen verstärkt. Bei 8% der Kranken kam es zu Haemoptysen oder Blutspuren im Auswurf; bei 5,2% von diesen hatten sich vor Behandlungsbeginn Haemoptysen ereignet, bei 2,8% war es zum erstenmal vorgekommen. 59 wurden aufgenommen mit Haemoptysen in der Vorgeschichte und 33 wurden aufgenommen wegen Haemoptyse. Nur bei 15 von 92 (16,3%) kam es zur Haemoptyse im Verlauf der Behandlung und bei den meisten von ihnen im ersten Trimester der Behandlung. Bei den 8 (2,8%), bei denen es im Verlauf der Behandlung zum erstenmal zur Haemoptyse kam, konnte die Blutung vorgefallen sein veranlasst durch die Natur der Krankheit, waren es doch sämtlich weit fortgeschrittene Fälle, 3 mit Siliko-Tuberkulose, oder zu erklären durch aussergewöhnliche Regsamkeit wie Trinken usw., und nicht unbedingt als Ausdruck der Wirkung von INH. Offenbar setzt das Mittel entschieden das Vorkommen von Haemoptysen bei tuberkulösen Patienten herab.

2. Keine andere Blutung (renal, rektal usw.), die auf die Chemo-Therapie zu beziehen gewesen wäre, wurde während der Untersuchung bemerkt.

3. Es bestand ein normales Vorkommen von operativen und postoperativen Blutungen mit einer Ausnahme, bei der der Mechanismus nicht zu erklären war.

4. Laboratoriumsuntersuchungen von Gerinnungszeit, Blutungszeit und Prothrombinzeit und die Auszählung von Blutplättchen vor und während der Behandlung zeigte Variationen innerhalb physiologischer Grenzen ohne eine bestimmte Tendenz oder Schema.

5. Capillardurchlässigkeit war normal in 79,2% und erhöht in 20,8%. Jedoch lag nur in 12,5% keine bestimmte Erklärung für die Erhöhung der Durchlässigkeit vor, und in diesem Falle konnte die Chemo-Therapie als einer der möglichen Faktoren angesehen werden. Weitere Untersuchungen werden angeregt.

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Pulmonary Adenomatosis Versus Bronchiolar Carcinoma*

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Introduction

The so-called alveolar cell tumors of lung, variably known as pulmonary adenomatosis, bronchiolar carcinoma, and many other names, are, indeed, one of the most controversial diseases in the history of modern medicine! They are primary tumors of human lungs of unique histologic features, and constitute an interesting pathologic group open to constant debates and speculations. Indeed, question has once been raised as to whether or not this group of tumors actually represents true "newgrowths"—however, current opinions seem no longer to cast any doubt.

Primary lung tumor was first described by Malassez[1] in 1876. In 1907, Helly[2] first observed a multiple nodular bilateral tumor in a 43-year old woman, which he termed an "adenomatous growth." The observation by Bonne,[3] in 1939, of the morphological resemblance of Jaziekte disease in sheep to certain cases of cancer of the lung in men has aroused renewed interest in this disease among medical investigators in this country.

There is reason to believe that pulmonary alveolar cell tumor may not actually be as rare as commonly thought. Over 200 cases already have been reported in the literature, and more are being discovered from time to time. Undoubtedly, a large number of cases may have been recognized but have never reached the literature. Likewise, it can be presumed that a considerable number of cases may have been missed entirely or mistaken for other diseases in the past, through lack of tissue pathology. Bronchogenic carcinoma, once deemed a very uncommon disease, is now already one of the most common and rapidly rising cancers of men. It is, therefore, quite possible that some day we may yet find alveolar cell tumor also a common disease either due to better case finding or due to actual increase in case incidence. It would, indeed, be interesting to find out just what effect those factors, which have caused a sharp rise in the incidence of bronchogenic carcinoma in recent years, would eventually have on the incidence of alveolar cell tumor of lung in the future.

Nomenclature

The naming of this group of tumors has been the center of chaos and confusion! Lack of accurate knowledge in the histogenesis has resulted in a wide variety of divergent names given to this disease by different authors. Liebow[4] alone has collected 36 names for this disease, not mentioning many more appearing in literature elsewhere. Names such

*Presented in abstract at the Joint Annual Meeting, Pacific Northwest Chapter, American College of Chest Physicians and Pacific Northwest Trudeau Society, November 12, 1954, Portland, Oregon.

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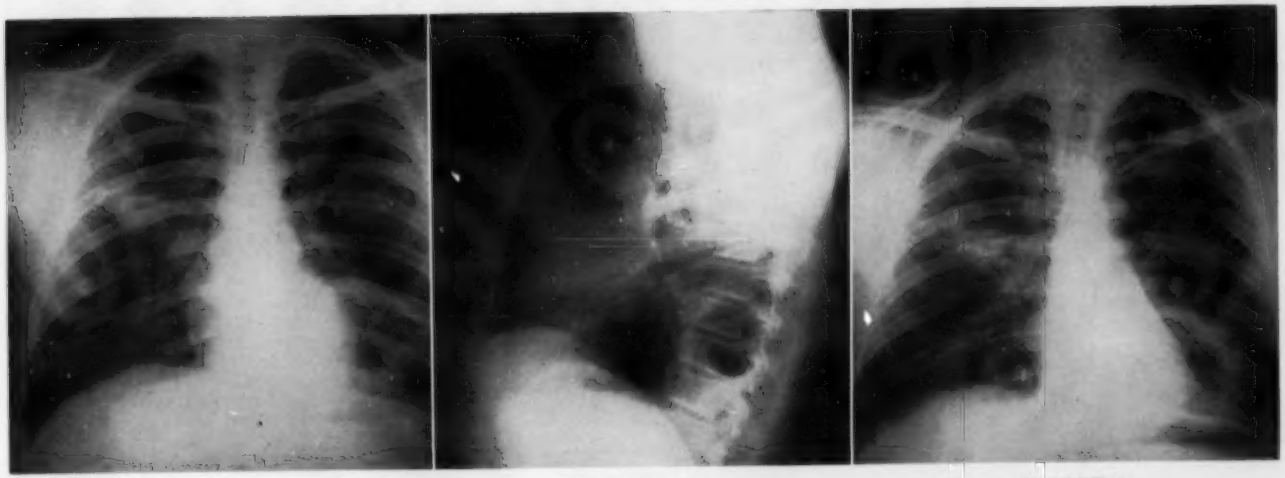

FIGURE 1

FIGURE 2

FIGURE 3

Figure 1 (Case 1): Admission film on August 8, 1952, shows bilateral infiltration with large excavation in left base.—*Figure 2* (Case 1): Left lateral film shows the huge cavity to be located in the posterior basal segment.—*Figure 3* (Case 1): Film on December 2, 1952, shows progression of disease with increase in size of cavity in spite of antimicrobial therapy.

as: "diffuse epithelial hyperplasia," "adenoma-like tumor," "primary diffuse epithelial carcinoma," "mucocellular papillary adenocarcinoma," "carcinosis," "Ewing's diffuse alveolar cancer," "malignant adenomatosis," "multicentric alveolar cell tumor," etc., are but a few of the numerous names suggested. However, in recent years, these names have been gradually narrowed down to a relatively few. The two most commonly mentioned are "pulmonary adenomatosis" and "bronchiolar carcinoma." The term "alveolar cell carcinoma," which denotes origin from lining cells of alveoli, is rejected by those who disclaim alveolar origin of the tumor; while the term "bronchiolar carcinoma," which denotes origin from lining cells of bronchioles, is equally opposed by those who reject bronchiolar origin of the tumor. However, during past years, number of people favoring bronchiolar origin seemed to be on the increase. On the other hand, "pulmonary adenomatosis" is probably still the most popularly used term, for the term itself is not involved in the controversy over origin of the tumor. "Adenomatosis," which literally means "increase in adenoma," or "glandular tissue overgrowth," without specifying innocence of malignancy, is disagreeable to those who feel that the word seems to imply a benign process and, therefore, has tendency to mislead one to regard all adenomatoses as benign tumors. Swan,[5] elected the term "adenomatosis," while Storey and coworkers,[6] opposed "adenomatosis" in favor of "bronchiolar carcinoma." So far, no common agreement has yet been reached on a suitable name for this disease acceptable to all.

Etiology

The etiology of pulmonary adenomatosis is still obscure. However, all present available evidences seem to point to a specific response to certain nonspecific irritants as the probable cause. Chronic irritation of the lung

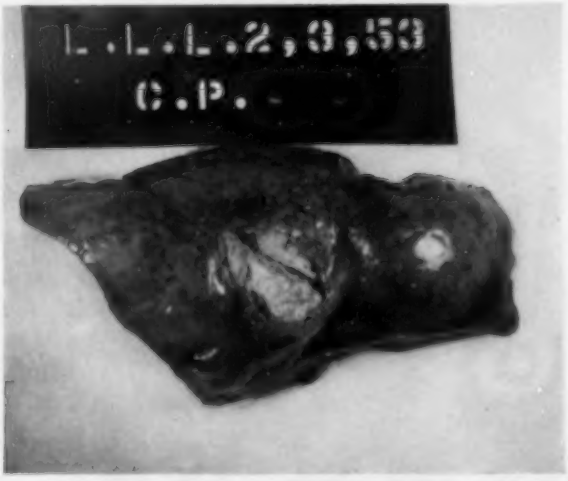

FIGURE 4: (Case 1): Left lower lobe resected on February 3, 1953, shows extensive diffuse hepatization with large excavation.

caused by repeated episodes of respiratory infections could, perhaps, in some cases, serve as the trigger mechanism in setting off the neoplastic process. Jagziekte disease in sheep, which closely resembles human pulmonary adenomatosis histologically, is said to be an infectious disease caused by, or associated with, a certain specific virus which acts as inciting factor. There is, however, no evidence that human pulmonary adenomatosis is an infectious disease associated with a virus.

Pathology

Pulmonary adenomatosis, or bronchiolar carcinoma, has its initial in the peripheral portion of the lung without involvement of major bronchi. Grossly, it is usually in the form of either a diffuse nodulation or a confluent consolidation simulating hepatization in pneumonia. Microscopically, the most common characteristic pictures are: alveolar proliferation of nonciliated columnar, or cuboid, mucus-producing epithelial cells, which form papillary projections into lumen of alveoli. Histologically, in the majority of cases, these cells often present all the features of benign hyperplasia and metaplasia, without anaplasia. Definite malignant changes with mitotic figures are seldom observed. Distant metastases are rare, although local or regional metastases are not uncommon. Cases have been reported where both benign and definitely malignant cells were seen side by side

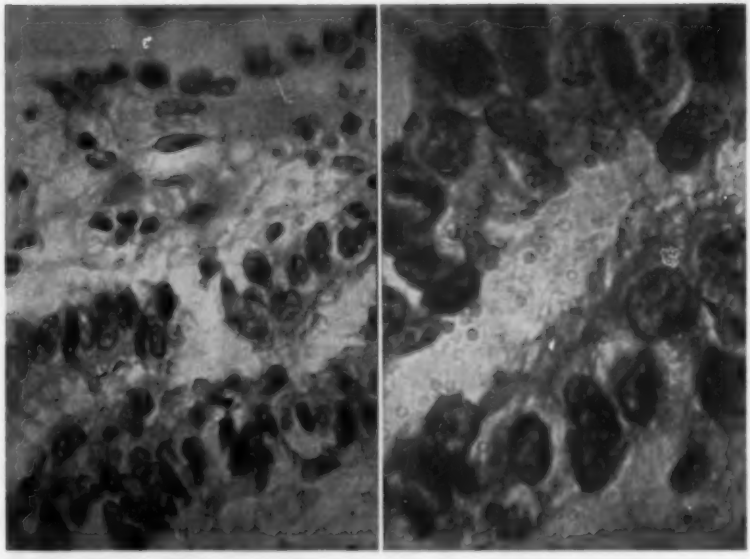

FIGURE 5 FIGURE 6

Figure 5 (Case 1): Microscopic section under high power reveals alveolar proliferation of benign-appearing columnar and cuboid cells.—*Figure 6* (Case 1): Microscopic histology under high power oil immersion shows mucin-containing cells with deeply-stained oval nuclei showing no mitosis.

in same tumor sections. In such instances, the change from benign to malignant state may be either gradual or abrupt. Thus, it makes one wonder whether these so-called alveolar cell tumors may not actually start as a benign hyperplasia which readily undergoes malignant degeneration, in certain number of cases, to transform into frank carcinoma.

Classification

It is questionable whether all alveolar cell tumors belong to one single disease, different variants of one disease, or even different diseases. Paul and Ritchie[7] believe adenomatosis must be regarded as a "pre-cancerous lesion." Drymalski and coworkers[8] thought pulmonary adenomatosis was a relatively benign variant of the so-called alveolar cell carcinoma, and was potentially capable of developing all the characteristics of malignancy. Swan[5] classified adenomatoses into "pulmonary adenomatosis" for the benign variety, and "cancerous adenomatosis" for the variety that metastasizes in addition. Abbott[9] described pulmonary adenomatosis and alveolar cell carcinoma as two separate diseases, but concluded that, "because of similarity of microscopic picture in the two diseases, it is easy to postulate that pulmonary adenomatosis may be transformed into the definitely malignant alveolar cell carcinoma." Grahm was strongly convinced that all pulmonary adenomatosis should be regarded as primary carcinomas of the lung of multicentric origin. On the other hand, authors like Watson and Smith,[10] Storey et al[6] and Stewart, prefer to group all these tumors under one name: bronchiolar carcinoma. Whether pulmonary adenomatosis is a benign hyperplasia, a pre-cancerous lesion, or a frank carcinoma is a matter that should be left to the pathologists to settle. However, it seems questionable whether we can honestly and justifiably, without changing our present concept and definition of malignancy, regard every

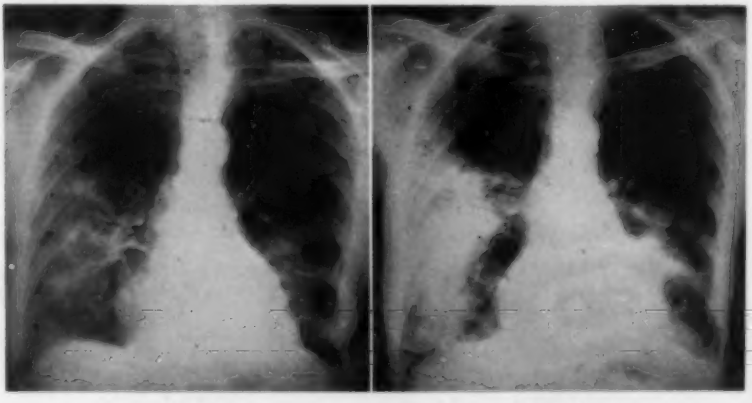

FIGURE 7 FIGURE 8

Figure 7 (Case 2): X-ray on January 30, 1953, shows considerable non-resolving infiltrations bilaterally.—*Figure 8* (Case 2): Film in November 1953, shows marked progression of disease bilaterally following repeated episodes of pneumonitis.

pulmonary adenomatosis as an outright carcinoma, when, histopathologically, majority cases show only alveolar proliferation of "histologically-benign," mucus-producing, columnar epithelial cells, which are well differentiated without mitotic figures and have little tendency to metastasize to distant organs. The occasional findings of benign hyperplasia alongside definitely malignant changes in the same tumor makes one wonder if we are not faced with a disease of transition nature bordering between benignancy and malignancy, which, if thoroughly understood, could shed light on the inner mystery of malignant degeneration of cells.

Histogenesis

The histogenesis of pulmonary adenomatosis, or bronchiolar carcinoma, is still highly controversial. The main argument, however, appears to be centering on the site of origin of this tumor—since normal histology of pulmonary alveoli is still debatable. The inability to demonstrate normal alveolar epithelium histologically has led many investigators to question the alveolar origin of this tumor. However, investigators like Miller, Bremer, and Swan maintained that pulmonary alveoli have true lining epithelium which is continuous. This is further supported by the observation that, in certain chronic pathologic processes of the lung, the outpouring of exudate behind the alveolar investment renders the lining epithelium "peeled off" to become demonstrable. Some investigators believed that the alveoli are lined with fetal epithelium which becomes attenuated following distention of the lung after birth, while other investigators claimed alveoli contain two kinds of cells: one an epithelial

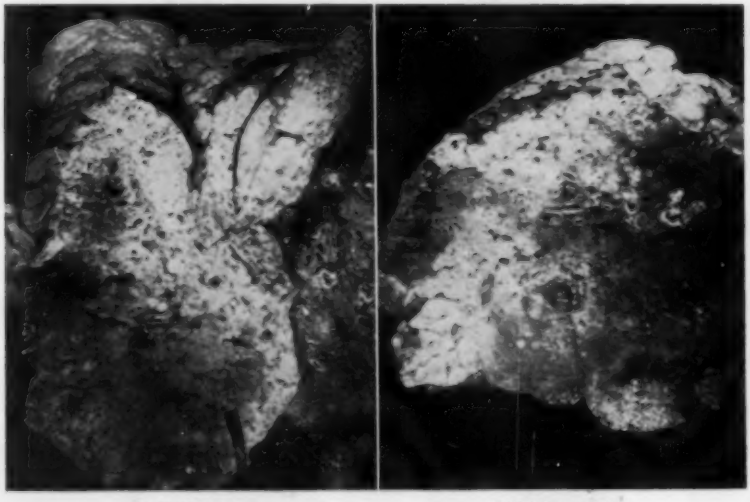

FIGURE 9 FIGURE 10

Figure 9 (Case 2): Right lung at autopsy shows extensive suppurative pneumonitis superimposed on diffuse nodular tumor.—*Figure 10* (Case 2): Left lung at postmortem shows same extensive lesion in lower lobe.

lining cell, and the other a phagocytic mesenchymal cell. On the other hand, Fried, Loosli, Bloom, and Lang claimed that pulmonary alveoli have no true lining epithelium, and that the capillaries are supported in a ground substance containing occasional mesodermal phagocytes, or septal cells of mesenchymal origin. Bell, Wood, Sims, and Ikeda were of the opinion that septal cells, derived from desquamated fetal epithelium left attached on septal walls, are epithelial in nature, and that these may proliferate in time of stress and strain to give rise to alveolar cell tumor. Swan[5] believed that, "a continuous alveolar lining probably exists, and that in no instances could the available evidence be interpreted as indicating that the alveolar investing cells arise from the bronchi by extension." He also concluded that, "cells which line the alveoli in many pathologic conditions have the same origin as cells which are present in the so-called alveolar cell tumor."

On the other side, Herbut[11] believed alveolar cell tumor arises from the basal cells of terminal bronchioles, to form either columnar or cuboid epithelial cells, and these extend downward to line the alveolar septa due to their inherent property to line cavity. Richardson[12] observed no pathologic change in either surrounding alveoli or bronchioles, and, therefore,

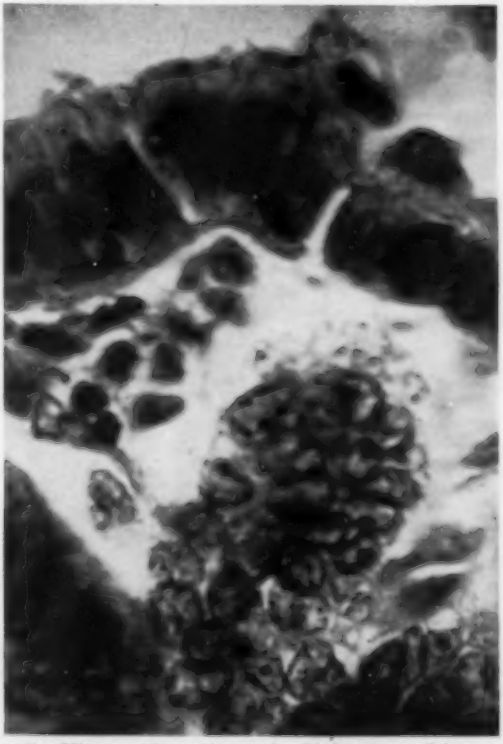

FIGURE 11 (Case 2): Microscopic section under high power oil immersion shows hypertrophic tall columnar cells with large and deeply-stained nuclei which show no mitosis.

regarded the origin from bronchiolar epithelium to be the more probable. Drymalski and coworkers[8] thought bronchiolar origin should be given preferential consideration. Gepts[13] observed, in a case of pulmonary adenomatosis, embryological abnormalities in the form of bronchiolar diverticuli, which he ventured to suggest as the probable site of origin of the tumor. In short, the main arguments in favor of bronchiolar origin are: (1) Alveoli have no true lining epithelium to give rise to tumor, (2) tumor cells closely resemble lining cells of normal bronchioles, and (3) frequently tumor cells are seen to extend downward from bronchioles into alveoli. On the other hand, the same arguments in favor of alveolar origin are: (1) Alveoli do have a continuous lining epithelium in the form of an investment, (2) frequently cells in frank alveolar cell carcinoma are quite dissimilar, histologically, to lining cells of normal bronchioles, and (3) conceivably, tumor cells could have extended upward from alveoli into bronchioles. Suffice it to say, the final answer to the origin of this tumor is, evidently, still far from being settled. In any event whether alveolar cell tumor is of epithelial origin or mesothelial origin is, in the opinion of some authors, of no particular importance, as one germ layer can, under certain abnormal conditions, form tissues normally specific for the other germ layer.[14] Furthermore, whether the tumor originates in the alveoli or in the terminal bronchioles is probably merely academic, as, according to observation of Waddell,[15] the lining cells of terminal bronchioles may, in themselves, be of mesodermal origin too.

Centricity of Origin

Debates are still raging as to whether pulmonary adenomatosis, or bronchiolar carcinoma, is of multicentric origin, as majority of authors used to believe, or of unicentric origin, as some recent authors have advocated. As yet there are still no convincing evidences offered by either side to substantiate their respective claims. Bell[16] pointed out that "hyperplasia" of alveolar epithelium may give rise to localized or diffuse growths which may form "metastases." The proponents of unicentricity theory contend that the tumor arises from one single primary center, and then from there it spreads to other portions of the lung, or opposite lung, by means of "metastases" through blood stream, lymphatic channels, or air passages, resulting in multiple foci of growths. The so-called "aerial metastases" through bronchogenic dissemination and implantation of desquamated tumor cells emboli in the alveoli sounds logical indeed, but remains yet to be proved beyond doubt. The recurrence of new lesions in contralateral lung, months or years following complete extirpation of tumor from one lung, is one of the points difficult to reconcile under unicentricity theory. Furthermore, under normal circumstances, hypertrophy and hyperplasia of tissues in an organ can take place simultaneously at several different foci; so that, if one were to assume that pulmonary adenomatosis essentially begins as a hyperplasia of epithelial cells in the lung, then its multicentricity of origin would, indeed, be difficult to rule out.

Clinical Features

Clinically, the alveolar cell tumor is a slow growing tumor, but a steadily progressive one, ending invariably in death of the patient when untreated. Death is usually due to asphyxia caused by progressive drowning-out of lung tissues by tumor tissues, or, more frequently, due to superimposed concurrent secondary pneumonitis. Unfortunately, there are no signs or symptoms pathognomonic of the disease. Strance[17] emphasized the clinical observation of chronic cough productive of large amount of sputum, dyspnea out of proportion to cough and sputum, and absence of hemoptysis, as the characteristics of this disease. The symptom of bronchorrhea with huge quantity of frothy, stringy, glairy, tenacious mucoid sputum is probably the most characteristic and suggestive; and, when present, should arouse suspicion of this disease.

There is no question that, in spite of its apparent benign histopathology, this tumor behaves clinically like a malignant tumor in that it kills by relentless growth. There are good reasons to regard it as perhaps even more hopeless and frustrating than the more malignant bronchogenic carcinoma because of the early appearance of multi-foci of growths. Bilateral involvement or multi-lobar involvement usually already exists by the time the tumor is discovered, rendering surgical treatment less effective, or even futile. And, because of the highly differentiated character of its cells, this tumor does not respond well to x-ray irradiation therapy.

Diagnosis

Diagnosis of this disease in the past was based mainly on autopsy materials or surgical specimens, rarely on clinical findings. With increased knowledge of and better acquaintance with this disease, clinical diagnosis can be made nowadays with increasing accuracy from suggestive symptoms, x-ray findings, and cytology of sputum. Bronchoscopy usually does not help. Cytologic study of sputum is based on the findings of clumps of columnar epithelial cells having free borders on one side. X-ray findings are nonspecific. The disease can be easily confused with pulmonary tuberculosis, especially if there are bilateral lesions with cavitation.

Treatment

Treatment for pulmonary adenomatosis, or bronchiolar carcinoma, so far has been disappointing. Surgical resection seems to be the only measure offering some hope for survival in selected cases, provided done early. Radiotherapy is of little value. Present trend with regard to extirpative surgery for this disease appears to be leaning toward moderation, with lobectomy being recommended as the minimal resection, and pneumonectomy for more extensive unilateral lesions.

Report of Cases

Case 1: C. P., a 45 year old white male, was admitted to Central Washington Tuberculosis Hospital on September 9, 1952 with a history of onset of bothersome productive cough three months prior to admission. Cough progressively became worse, with increasing amounts of frothy, stringy, glairy, mucoid sputum, which averaged several cupfuls a day, but unaccompanied by fever, night sweats, chest pain, or hemoptysis. Weight loss was ten pounds in three months, with increasing fatigue and shortness of breath. Two sputum specimens sent to public health laboratory for examination by his outside private doctor were reported back as positive for acid-fast bacilli on smears. Therefore, patient was admitted as a presumptive case of pulmonary tuberculosis.

On admission, all laboratory tests were essentially negative. X-ray of chest showed extensive bilateral disease with huge cavitation in the left lower lobe. Patient was put on routine antimicrobial therapy for tuberculosis. Repeated sputum tests, meanwhile, failed to yield tubercle bacilli either on smears or on cultures. Follow-up x-ray films showed continuous progression of disease. Two bronchoscopies and several cytologies of sputum were all negative. Therefore, a left exploratory thoracotomy was carried out on February 3, 1953.

At operation, entire left lung was found to be extensively involved, but was surprisingly free from adhesions. Entire left lower lobe showed diffuse consolidation, simulating red hepatization in pneumonia, with large excavation located in the posterior basal segment. Left upper lobe showed scattered patches of pneumonic consolidation. No enlargement of hilar nodes was noted anywhere, nor any sign of peribronchial changes. A complete left lower lobectomy was performed mainly to eradicate the chief source of sputum.

Microscopic sections of surgical specimen revealed diffuse and focal proliferation of epithelial cells lining the alveoli, sometimes to the exclusion of lumens. These cells were tall columnar, but sometimes pear-shaped, and had much mucin inside. Occasionally they showed pseudostratification; and sometimes the hyperplasia was so extreme that papillary structures projected out into and completely filled alveolar lumens. These cells were seen to spring from the inner surfaces of the alveolar lining walls. Cell nuclei were oval and of medium size and showed no mitosis. Diagnosis, as concluded by the pathologist, was: "Pulmonary Adenomatosis."

Patient did well for a while following surgery, with considerable diminution in cough and sputum. Soon after discharge he again resumed a downhill course, with increasing symptoms and relentless progression of disease of lung bilaterally. He received courses of x-ray treatment outside without decisive benefit. Finally he died of lobar pneumonia on October 16, 1953. Autopsy findings confirmed the diagnosis of pulmonary adenomatosis.

Case 2: D. B., a 71 year old white woman, was referred to our hospital in September of 1953 as an outpatient for consultation and sputum study. History revealed repeated episodes of respiratory infections and pneumonia manifested by high fever and productive cough since January of 1953, necessitating hospitalization several times. Symptoms relieved with antibiotics each time, to recur soon after cessation of treatment. Follow-up x-ray of the chest showed persistent nonresolution of pulmonary lesions bilaterally. Cough became progressively worse, with increasing quantity of mucoid expectoration, which amounted to several cupfuls a day. Patient had no hemoptysis, but had progressive weight loss, general weakness, and occasional chest pain between scapulae.

In November of 1953, patient sent in one big jarful of sputum for examination and culture. From the character of the sputum, a diagnosis of "pulmonary adenomatosis" was immediately made and suggested to her private doctor. All the sputum tests, including previous ones, were all negative for acid-fast bacilli on smears and cultures. Cytologic study of sputum also failed to disclose any tumor cells by Papanicolaou's technique. Because of her age, patient was treated and followed at home. On March 22, 1954, she finally died of acute pneumonitis following two days of illness.

At autopsy, both pleural cavities were surprisingly free from any inflammatory adhesions. Both lungs showed scattered nodular lesions and extensive consolidation, especially in the left lower lobe, right middle lobe, and right lower lobe. Numerous tiny abscesses were noted, suggestive of suppurative pneumonitis. All major bronchi were opened and showed no involvement. Only a few slightly enlarged mediastinal nodes were found, which, however, showed no tumor tissues grossly on section.

Microscopic examination of lung sections showed complete obliteration of pulmonary architecture due to presence of large and small, closely adjacent papillary structures having vascular fibrous stroma and being lined on each surface by single layers of tall, seemingly, orderly but hypertrophic, columnar epithelial cells. Such cells were not ciliated and had mucin in their peripheral cytoplasm. The nuclei, though large and deeply

stained, were fairly regular and in the basilar or midportion of the cells. Mitoses were not seen in them. Extensive suppurative pneumonitis was noted, the inflammatory reaction having overshadowed the neoplastic. No direct transition between normal epithelium of bronchial walls and the neoplastic cells was observed. In one section of the mediastinum nodes, similar tumor cells were found. The pathological diagnosis as given by the pathologist on this case was: "Bronchiolar Carcinoma of Lung, Bilateral, Multicentric."

Addendum: Since submission of this paper for publication, a third case of alveolar cell tumor was diagnosed from surgical specimen and confirmed at autopsy. The final diagnosis given to this case by the same pathologist was that of alveolar cell carcinoma.

SUMMARY

1. Lack of accurate knowledge in the histogenesis has resulted in a wide variety of divergent names given to the so-called alveolar cell tumors of lung, which are primary lung tumors of unique histopathologic features, and which may someday prove to be not a rare disease.

2. Of the two most commonly used names, "bronchiolar carcinoma" is opposed by those who reject bronchiolar origin of the tumor, while "pulmonary adenomatosis" is opposed by those who claim the term implies a benign process and is misleading. As yet no satisfactory name has been agreed upon.

3. Whether pulmonary adenomatosis is a benign lesion, a pre-cancerous lesion, or a definitely malignant lesion, is by no means a settled matter. Could it be that we have here a disease of transition nature bordering between benignancy and malignancy, which, if thoroughly understood could open the door to the mystery of malignant changes of cells?

4. The controversy between alveolar origin and bronchiolar origin of the tumor is still raging, but the issue is probably merely of academic interest, as both alveolar lining cells and bronchiolar lining cells may, perhaps, in themselves, be of same origin.

5. Multicentricity of origin of pulmonary adenomatosis has to be ruled out first before unicentricity theory can be established, if the growth could be regarded as essentially a relentless alveolar proliferation of histologically-benign epithelial cells in the beginning.

6. Clinically, pulmonary adenomatosis is perhaps even more hopeless and fatal than the more malignant bronchogenic carcinoma due to its frequent multifoci of growths and its tendency to early bilateral involvement, which renders surgical treatment less effective.

7. Importance of early clinical diagnosis is emphasized, if patient is to be saved. Disease can be easily confused with pulmonary tuberculosis, especially if bilateral involvement with cavitation.

8. Two cases presented: one diagnosed as "pulmonary adenomatosis" from surgical specimen, the other as "bronchiolar carcinoma" from autopsy specimen—both diagnoses by the same pathologist.

RESUMEN

1. La falta de conocimiento exacto sobre la histogénesis ha dado lugar a la gran divergencia de nombres dados al llamado carcinoma alvéolo celular, que son tumores primitivos del pulmón de características histológicas

únicas, y que puede alguna vez considerarse como una enfermedad no determinada.

2. De los dos nombres más comunmente usados, "carcinoma bronquiolar" se opone a los que no le reconocen origen bronquial en tanto que "adenomatosis pulmonar" se opone a los que sostienen que el término implica un proceso benigno y esto es desconcertante. No hay aún acuerdo sobre el nombre.

3. Si la adenomatosis pulmonar es una lesión benigna, una lesión precancerosa o definidamente maligna, no es una cuestión transada.

Podría ser que se tratase de una enfermedad de transición enlos límites lo benigno y lo maligno que si se comprendiese completamente quizás abriría la puerta hacia el misterio de los cambios malignos en las células?

4. La controversia entre el origen alveolar y el bronquiolar del tumor está aún en pie, pero el resultado sería sólo de importancia académica, puesto que tanto las células de revestimiento alveolar como las de revestimiento bronquiolar son del mismo origen probable.

5. El origen multicéntrico de la adenomatosis pulmonar tendría que ser descartado antes de establecer una teoría unicéntrica, si el tumor pudiese ser visto como una proliferación alveolar incontenible de células epiteliales histológicamente benignas al principio.

6. Clínicamente, la denomatosis pulmonar es ún más desesperada y fatal que el carcinoma bronquiogénico más maligno debido a la multiplicidad de sus focos de neoplasia y su tendencia a invasión bilateral lo que hace el tratamiento quirúrgico menos efectivo.

7. Se recalca la importancia del diagnóstico clínico temprano si el paciente ha de salvarse. La enfermedad se confunde fácilmente con tuberculosis pulmonar especialmente si hay invasión bilateral y escavación.

8. Se presentan dos casos: uno diagnosticado como "adenomatosis pulmonar" del espécimen quirúrgico y el otro como "carcinoma bronquiolar" después de autopsia. Ambos por el mismo anatomopatólógo.

RESUME

1. L'absence de connaissances approfondies dans l'histogénèse a fait qu'une grande variété de noms différents a été appliquée aux soi-disant tumeurs alvéolaires du poumon. Il s'agit en fait de tumeurs pulmonaires primitives de structure histopathologique définie. On pourra un jour démontrer qu'il s'agit bien d'une affection particulière.

2. L'un des deux noms les plus communément employés, "carcinome bronchiolaire," est rejeté par ceux qui ne reconnaissent pas l'origine bronchiolaire de la tumeur, tandis que "adénomatose pulmonaire" est rejeté par ceux qui proclament que le terme implique à tort un processus bénin. Jusqu'à présent, aucun terme satisfaisant n'a été accepté.

3. Rien ne permet d'affirmer que l'adénomatose pulmonaire est une lésion bénigne, une lésion précancéreuse ou une lésion vraiment maligne. Il est possible que nous ayions de la bénignité et de la malignité. Si sa

nature véritable était bien établie, elle pourrait percer le mystère de l'apparition de la malignité cellulaire.

4. La controverse qui opposa les tenants de l'origine alvéolaire et de l'origine bronchiolaire de la tumeur est encore d'actualité. Elle est vraisemblablement sûrement académique et les deux termes s'appliquent sans doute à un phénomène identique.

5. La théorie de la multiplicité de l'origine de l'adénomatose pulmonaire doit être réglée avant qu'une théorie d'origine unique puisse être établie, si l'on peut admettre que le développement de la tumeur est essentiellement caractérisé par une prolifération alvéolaire de cellules épithéliales histologiquement bénignes au début.

6. Cliniquement, le pronostic de l'adénomatose pulmonaire est peut-être et plus sûrement fatal que le carcinoma bronchique le plus malin. La cause en est due à ses foyers évolutifs multiples et à sa tendance à la bilatéralisation précoce, qui rend moins efficace le traitement chirurgical.

7. Les auteurs insistent sur l'importance d'un diagnostic clinique précoce, si l'on veut sauver le malade. L'affection peut être facilement confondue avec la tuberculose pulmonaire surtout s'il y a une atteinte bilatérale avec processus cavitaire.

8. Deux cas sont rapportés: l'un avait été considéré comme une adénomatose pulmonaire après examen d'ùne pièce d'exérèse chirurgicale révélée après intervention, l'autre comme un carcinome bronchiolaire après examen d'un prélèvement fait lors de l'autopsie. Los deux diagnostics ont été faits par le même anatomo-pathologiste.

ZUSAMMENFASSUNG

1. Das Fehlen einer genauen Kenntnis der Histogenese hat eine grosse Vielzahl von abweichenden Namen zur Folge gehabt, die Verwendung fanden für die sogenannten Alveolar-Zell-Tumoren der Lunge, die primäre Lungentumoren von bemerkenswerten histo-pathologischen Grundzügen sind und die sich eines Tages als keineswegs seltene Krankheit herausstellen können.

2. Von den beiden am häufigsten gebrauchten Namen findet das "bronchioläre Carcinom" eine Gegnerschaft bei denen, die einen bronchiolären Tumorursprung verwerfen, während die "pulmonale Adenomatose" auf Gegnerschaft bei denen trifft, die behaupten, der Ausdruck unterstelle einen gutartigen Prozess und sei irreführend. Bis jetzt ist noch keine Einigkeit über eine befriedigende Bezeichnung erzielt worden.

3. Ob die pulmonale Adenomatose eine gutartige Veränderung darstellt oder eine praecanceröse oder eine definitiv bösartige Veränderung, ist keineswegs eine entschiedene Tatsache. Wäre es möglich, dass wir hier eine Krankheit transitorischer Natur vor uns haben an der Grenze zwischen Gut- und Bösartigkeit, die, versteht man ihr Wesen, imstande ist, die Tür zu öffnen zum Mysterium der bösartigen Zellverwandlung?

4. Die Kontroverse zwischen alveolärem Ursprung und bronchiolärem Ursprung des Tumors ist noch heftig im Gang, aber die Streitfrage ist von

rein akademischem Interesse, da beide, die alveolären Randzellen und die bronchiolären Randzellen vielleicht gleichen Ursprungs sind.

5. Die Multizentrizität der Entstehung der pulmonalen Adenomatose muss zuerst ausgeschlossen werden, ehe die unizentrische Theorie begründet werden kann, wenn das Wachstum zu Anfang als eine wesentlich unaufhaltsame Proliferation von histologisch gutartigen epithelialen Zellen betrachtet werden könnten.

6. Klinisch ist die pulmonale Adenomatose vielleicht sogar noch hoffnungsloser und letaler als die mehr bösartigen bronchiogenen Carcinome infolge ihres häufig multifokalen Wachstums und ihrer Tendenz zu frühzeitiger bilateraler Beteiligung, wodurch die chirurgische Behandlung wenig wirksam wird.

7. Die Wichtigkeit der klinischen Frühdiagnose wird betont, soll der Kranke gerettet werden. Die Krankheit kann leicht mit Lungentuberkulose verwechselt werden, besonders bei beidseitiger Beteiligung mit Cavernisierung.

8. Zwei Fälle werden vorgewiesen: der eine diagnostiziert als "pulmonale Adenomatose" durch das Operationspräparat, der andere als "bronchioläres Carcinom" aus Sektionsmaterial—beide Diagnosen vom gleichen Pathologen.

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Repeated Antimicrobial Therapy in Children: The Problem of its Effectiveness and Safety

A Ten-Year Survey of the Practice of Simultaneous and Successive Combination Therapy*

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The discovery of effective and powerful antimicrobial chemicals has had a twofold impact on the world. On the one hand it has substantially reduced the total number of microbial organisms by direct bactericidal action, and among the surviving pathogenes it has caused a still problematical change in their relationship to their environment.

The following investigation into the effects of repeated antibacterial therapy during 10 years at Milwaukee Children's Hospital has as its object the assessment of the actual results obtained by applying the chemotherapeutical and antibiotic agents, as they became available, by the entire attending pediatric, surgical and resident staff of our hospital, without any strict centralized overall therapeutic policy.

In evaluating this large clinical material with a great diversity of therapeutic programs and combinations we have tried to disassociate ourselves, temporarily at least, from the great temptations of overenthusiasm and of overskepticism which can be found so frequently in the literature pertaining to modern anti-infectious therapy.

The main reason for this attempt at arriving at some definite conclusions, by way of empiricism rather than scholasticism, is the appalling diversity of statements and opinions about indications and contraindications, bordering here and there on outright contradiction. The volume of literature in this particular field is such that even an approximation to a complete review is positively prohibitive. In the following paragraphs a selection of ambiguous, confusing and contradictory quotations will be given and not, to be sure, for the sake of criticism, but in order to illustrate the psychological impasse medical science is in, surrounded by a host of its own creations, trying to map the correct route to follow.

Digest of Pro and Con in Antimicrobial Literature

As an illustration of this contention as to volume I like to mention a recent article by Wesley W. Spink[1] on the limited subject of "Staphylococcal Infections and the Problem of Antibiotic-Resistant Staphylococci" with no less than 128 references. An attempt at anything approaching a complete bibliography would therefore have defeated the purpose of this survey right from the start.

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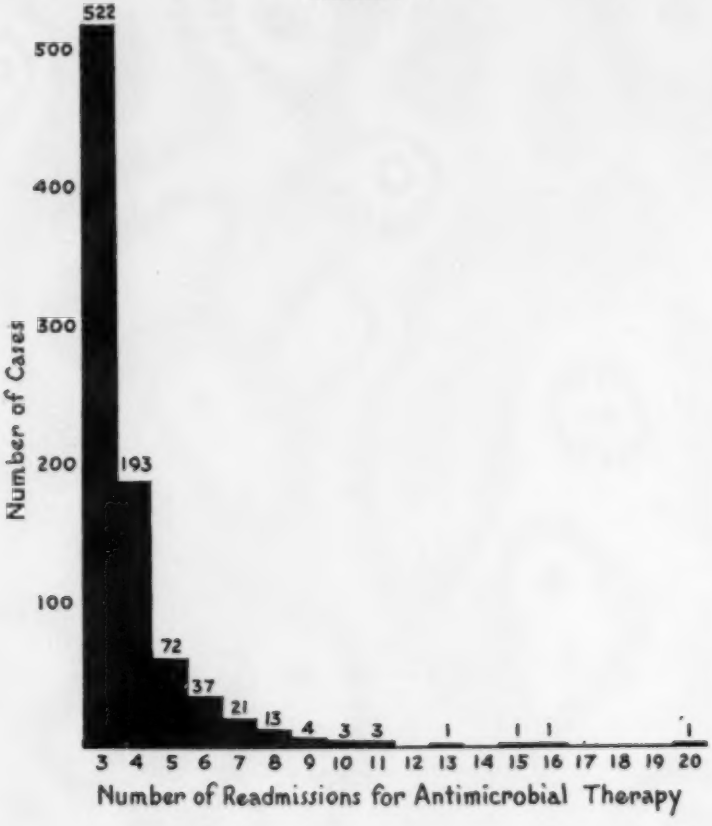
In the above article Spink concludes, "One of the greatest advancements in medical practice in the last decade has been the introduction of the antibiotics. The impact of these agents upon the course of many infections has been so remarkable that some diseases have been almost eliminated as serious entities." With regard to the phenomenon of bacterial drug resistance he points to old investigations by Paul Ehrlich and he goes on, "As aids in the prevention of chronicity of the infection and of protection against the appearance of resistant parasites, he (Ehrlich) suggested just what we have advocated for the treatment of staphylococcal sepsis, namely, energetic and aggressive treatment with a combination of drugs that had been selected on the basis of sensitivity tests carried out in the laboratory."

William H. Feldman,[2] on the other hand, formulates some serious doubts as to the wisdom of large-scale use of the various antibiotics. "We are well into an era of promiscuous therapeutics in which the per capita consumption of the newer chemotherapeutic substances is probably second only to aspirin . . . Although these newer medicaments are prescribed with therapeutic intent, they are, like most drugs, potentially poisonous." He

TABLE I



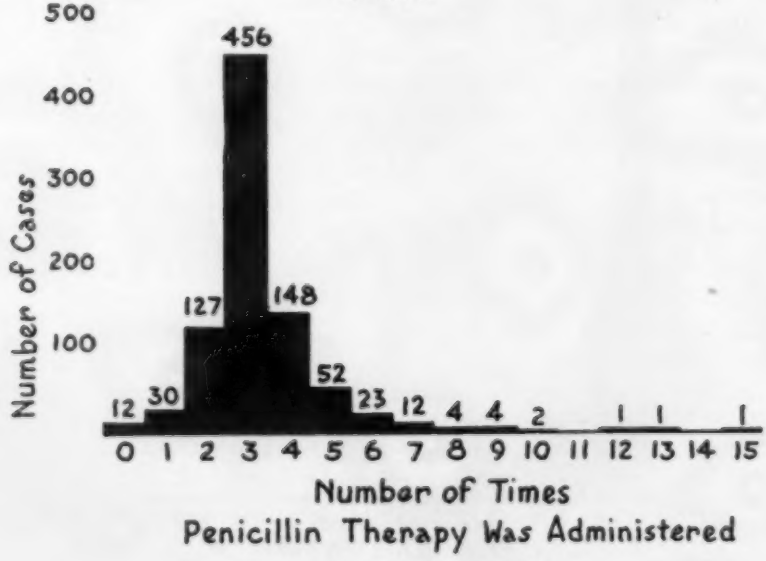
concludes as follows: "The substantial value of modern chemotherapeutic agents is recognized. When used with circumspection, many synthetic and antibiotic agents have life-saving potentialities." (Possibly the understatement of the century!) "However, many of these medicinals, if prescribed unwisely, are definitely hazardous. This is particularly true of agents having a broad antibacterial spectrum and in situations where chemotherapy is continued for prolonged periods of time."

Finland, Maxwell and Weinstein[3] cautiously state, "The fact that harmful effects may follow the use of these drugs should not discourage the physician from applying them when they are definitely indicated."

As to indications for prolonged antibiotic treatment there is at the present time a school that believes firmly in the rational of rheumatic fever prevention by continuous chemotherapy. Hamilton and co-workers[4] state, "A program of continuous prophylaxis to stave off intercurrent streptococcic disease appears thus far to be the best available method for the prevention of recurrent attacks of rheumatic fever." A still more fargoing program of streptococcal disease prophylaxis has been advocated by another research team[5] through year-round daily oral administration of 500,000 units of penicillin in rheumatic fever convalescents and the remark is added that there would be no purpose in continuing the practice of closing schools during streptococcal disease epidemics if the entire student body can, simultaneously, be given penicillin orally in the dose and for the period reported.

In a previous publication a Cleveland group[6] suggests that short term intermittent administration of a bactericidal drug, such as penicillin, may

TABLE II



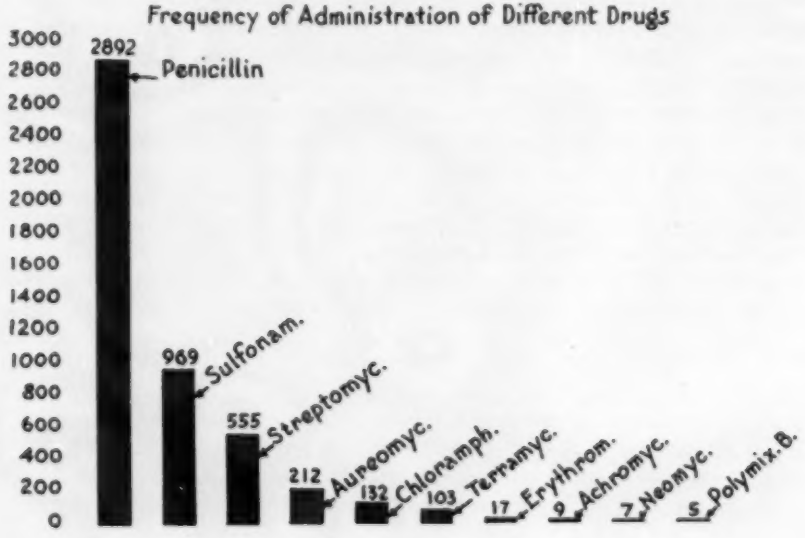
be an effective method for the prophylaxis of streptococcal disease and may have certain advantages over the continuous exhibition of suppressive agents such as the sulfonamides."

Elghammer[7] recommends that "the administration of penicillin should be continued into the convalescent period (of rheumatic fever) in order to prevent reinfection. In carriers, penicillin has been found very effective in eradicating streptococci from the oropharynx."

As to an extreme standpoint in the liberal use of antibacterial drugs the following quotation (Kempe)[8] serves as an example, "Recognition of family infection and treatment of the entire family, including those who are not sick, with the best antibiotics at hand ostensibly offers the best hope for the management and prevention of repeated reinfection from the family source of children who are chronically ill."

To offset this apparent overenthusiasm for wholesale use of antibiotics we may mention two representative articles which in an almost sweeping way deprecate the by now commonly accepted general use of these drugs. An editorial in the New England Journal of Medicine,[9] "Therapeutic Exuberance," approves of the antibiotics only "when the battle is critical or fraught with risk, but neither (as) a substitute for natural resistance and acquired immunity, nor a new invention outmoding the necessity for medical judgment." A still stronger dose of this sort of medical propaganda is contained in an article prepared by the Special Committee on Child Welfare of New York County Medical Society[10] in which it says, "Antibiotics, though invaluable for the treatment of certain inflammatory (?) conditions, have been unduly exploited, overused and abused . . . under no circumstances should a single dose be primarily prescribed. Dosage

TABLE III



should be continued until all symptoms and signs of infection have disappeared." But in the next paragraph we read, "It is conceivable that if the present trend of overdosing with the antibiotics continues, soon physicians may have little or nothing with which to combat the staphylococci."

Yet what specific conclusions to draw from such generalities of wisdom and warning is another question if we take a look at a different editorial in the *Journal of the American Medical Association* on "Continued Perils of Pneumonia and Influenza."[11] Here we read, "The death rate from pneumonia and influenza, which began to decline rapidly after the introduction of the sulfonamides some 15 years ago, has continued its downward trend as the result of widespread use of antibiotics."

This decline in the death rate, by the way, has been found by Muscato and this author[12] not to be due as much to a lower incidence or any prophylactic effect of the newer drugs, but almost entirely to their curative action. Only in secondary pneumonia, as a complication during the hospital stay of children, a sharp decline almost to the vanishing point became manifest thanks to the liberal use of antimicrobial agents as a hospital routine.

Jawetz and Gunnison[13] in their studies on antibiotic synergism and antagonism have complained that the number of combinations and permutations has become appalling. They have classified these drugs in two groups. Group I. Penicillin, streptomycin, bacitracin, neomycin. Group II. The several tetracyclines and sulfonamides. They consider the agents of Group I frequently synergistic, occasionally indifferent, never antagonistic. The members of Group II neither synergistic nor antagonistic, but simply additive. The addition of Group II to Group I drugs is warranted only if based on laboratory evaluation suggesting synergism.

References as to the presence or absence of such synergism can be found proving or disproving the benefits of any imaginable combination. Here are a few cases in point. Davis[14] found the combination of chloramphenicol and penicillin adequate in pneumococcal pneumonia. Kirby[15] and co-workers found among 10 strains of coliform bacilli isolated from patients with urinary tract infections 43 per cent to be resistant to streptomycin, 29 per cent to chlortetracycline and oxytetracycline, 2 per cent to chloramphenicol and 3 per cent polymyxin B. Denny and co-workers[16] compared the effects of penicillin, aureomycin, and terramycin on streptococcal infections and concluded that no one drug was consistently more effective than the other two. But they stated that from the standpoint of toxicity penicillin is the drug of choice. It also was more effective than the tetracyclines in short and long term eradication of streptococci from the throat.

Digest of Our Own Repeated Antimicrobial Therapy

Before attempting an interpretation of therapeutic results with repeated administration of antimicrobial drugs obtained in our own cases, it is fitting to present first our clinical material from the statistical point of view. This consisted of all patients who, during the 10 year period from 1944 until about midyear 1954, were admitted to the hospital three or

more times and had undergone during their hospital stay antibiotic or chemotherapy. The total number of cases thus reviewed was 872, while the total number of case histories scrutinized was 3158. In 552 cases there were three admissions with administration of various chemotherapeutical agents, 103 were admitted four times, 72 five times, 37 six times, 21 seven times, 13 eight times, four nine times, three 10 times, three 11 times, one 13 times, 15 times, 16 times and 20 times respectively (Table I). If we draw an arbitrary line between moderately and exceedingly frequent repetition of chemotherapy, we arrive at the figure of 157 cases who had 6 to 20 admissions for various forms of anti-infectious treatment.

It stands to reason that many of these children will have had more drug therapy for intercurrent diseases given to them as outpatients either at home or otherwise; therefore, the above figures for repeated chemotherapy represent only the minimum actually on record.

In order to characterize the type of clinical material of our survey the important point is that about every morbid condition of childhood prevalent in this general area is represented among these 872 patients. We have laid emphasis before on the absence of any overall policy in selection of cases and of therapy. This increases, in our opinion, the objective value of our clinical material because, in avoiding any preconceived therapeutic program, we are enabled to study what actually has happened to the practice of medicine in these fateful years with regard to childhood infections.

We proceeded to tabulate the pertinent data of each case history as follows:

> Name/Dates/Number of admissions/Age on first admission/Age on last admission/Diagnoses on each admission (1-2-3-4-5-6-etc.)/Types of chemotherapy (1-2-3-4-5-6-etc.)/Response (1-2-3-4-5-6-etc.)/Drug allergy.

The ages on first and last admission indicate the period of time over which the repeated drug administration was distributed. This varied, of course, from case to case and as illustration of extremes as far as the time element is concerned we may use the following examples:

A 13 month old girl with meningocele and urinary tract infection, readmitted for a total of 10 times over a period of 15 months. Surgery was performed on second admission. The following courses of drugs were used: Penicillin nine times, sulfonamides seven times, terramycin once, and chloramphenicol once. The child responded each time favorably and promptly to therapy, and at the age of 28 months she was discharged as recovered. There were no signs of drug allergy or idiosyncrasy.

A one month old premature weighing 3 pounds, 2 ounces, admitted eight times during 11 months with the diagnoses of acute enteritis, pyuria, upper respiratory infection, otitis media, hypoadrenalism, and pneumonia. Drug treatment consisted of penicillin seven times, streptomycin four times, sulfonamides two times. At the age of 12 months the child weighed 17 lbs. and was finally discharged in good health.

A newborn boy was admitted on the first day of life with imperforate anus for emergency surgery. On seven successive admissions several stages of corrective operations were performed. Upon the second admission there was complicating bronchopneumonia. Drug administration consisted of six courses of penicillin, five of streptomycin, five of sulfonamides, two of neomycin, one of chloramphenicol, terramycin, achromycin, and erythromycin respectively. At the age of two years seven months the child was discharged in good health and free from infections.

In contrast to these cases where repeat chemotherapy has been crowded into a relatively short space of time we may consider the following examples of long range treatment:

A one year nine month old girl was admitted with diagnosis of meningocele and congenital heart disease. Corrective surgery was performed on third and fifth admission. There was a sequence of urinary and respiratory tract infections, 20 hospital admissions all told over a period of more than five years, after which she was discharged in generally satisfactory condition. Chemotherapy consisted of 5 courses of penicillin, seven of sulfonamides, three of streptomycin, seven of aureomycin, two of chloramphenicol and two of terramycin. Sensitivity studies in the last year revealed a previously suspected bacterial resistance to penicillin and aureomycin. Yet, she finally made, after more than five years, a satisfactory recovery on repeated combination antibiotic therapy without untoward allergic side-effects.

A five month old boy was admitted with diagnosis of lobar pneumonia, readmitted as unresolved pneumonia with bronchiectasis. On third admission lobectomy was performed. There was a total of six admissions over a period of eight years and eight months. Drug therapy consisted of five courses of penicillin, two of sulfonamides, one of terramycin. On last admission studies showed complete sensitivity to penicillin. There was no allergic manifestation, and the end result was excellent.

These samplings of our large amount of material do not tell us much about the correctness or the drawbacks of this kind of therapeutic procedure. They do indicate, however, the actual antibiotic "facts of life," free from theoretical inhibitions, as they became established at Milwaukee Children's Hospital following the introduction of these drugs.

As it is physically impossible to report all the 3,158 case histories in detail, we shall proceed in presenting a breakdown of our material which should provide an insight into the overall repeat chemotherapy.

Table II demonstrates the overall frequency of administration of the different drugs, the result of which may be called an antibiotic popularity contest. It shows that penicillin is way out in front with 2,892, followed by sulfonamides 909, streptomycin (given mostly in combination with penicillin) 555, followed by the several tetracycline preparations.

Table III gives the number of times courses of penicillin were repeated. We find that only in 12 cases out of our total other agents were used to the exclusion of penicillin, while in exactly 100 cases five and more courses of penicillin were given.

It is difficult to enumerate or to classify our material from the diagnostic angle because just about the entire range of morbid conditions has been encountered. We already reported one case of prematurity. There were all kinds of congenital malformations, atresias of the intestinal tract or bile duct, heart lesions, cleft palates, clubfoot, microtia, etc. A considerable number of fibrocystic diseases of the pancreas was the object of repeat chemotherapy for obvious reasons. Besides, we find the innumerable varieties of respiratory tract, digestive tract, and urinary tract infections of different severity or even triviality repeatedly admitted and treated antibiotically.

Among the great number of respiratory diseases treated in this group, like acute laryngo-tracheo-bronchitis, lobar and bronchopneumonia, chronic bronchitis and bronchiectasis, we separated 72 cases which were labeled either asthmatic bronchitis or bronchial asthma. The question arose

whether antibiotic substances might have been in any etiological connection with the appearance of asthmatic manifestations or whether the use of these drugs seemed to have any untoward effect.

As it turned out, in 56 of these cases the diagnosis of asthmatic syndromes was made on first or second admission and antibiotic therapy was continued with good results. In 16 the diagnosis of asthma was entered on later admissions; however, in 15 the same medication was continued without ill effect. Only in one, an 11 month old infant, repeated administration of penicillin and streptomycin, while not aggravating the respiratory distress, seemed ineffectual against the underlying infection.

There were 13 who presented skin manifestations resembling allergic dermatitis, like atopic eczema associated with asthma, eczema with secondary infection, etc. This low number of cases may be due to the fact that the presence of an apparently allergic diathesis tended to discourage the use of potentially allergenic agents like molds. Yet in 11 antibiotic therapy was repeated for various reasons in the wake of a subsiding rash without causing exacerbation, while two cases developed assumingly allergic skin eruptions after prolonged and repeated medication (erythema multiforme, roseola) but entirely without any dramatic syndromes. This lack of menacing allergic incidents is in variance with reports about severe reactions following repeated penicillin administration in adults[17, 18] and we feel justified after scanning our 3158 case histories to stress this absence of severe side effects in childhood.

A more or less separate category was made up of patients admitted for major surgical procedures. There were 168 who underwent either operative procedures like appendectomy, at times following several courses of antibiotic treatment for acute appendicitis or periappendiceal abscess. Others were cases of atresia or stenosis of the intestinal tract and bile duct as previously mentioned, cardiac surgery, pulmonary lobectomy, etc.

However, the largest number of our surgical group, 113, was made up of orthopedic cases, including congenital malformations of the skeleton, postpoliomyelitic deformities for corrective surgery, cases of traumatic surgery, plastic surgery like skin grafting following burns, furthermore cheilo-uranoplastic operations, otoplastic corrections, and finally 52 tonsillectomies, eight dental extractions with preoperative and postoperative chemotherapy. (These latter 60 not included among the above 168).

It seems remarkable that all the various attending surgeons on our staff, regardless of their specialty, appear to have almost unanimously agreed on including anti-infectious drug therapy in their preoperative and postoperative routine. This could not possibly have been the case, if continuous experience would not have taught them that the advantages of preventing intercurrent infections by far outweighed the occasional episodes of side-reactions. This reviewer, therefore, assumed only the pleasant task of verifying at the hand of the hospital records the practical absence of severe drug idiosyncrasies or allergies.

Another more problematic aspect of simultaneous and successive anti-

microbial therapy is the degree of effectiveness of the different agents, single or in combination, at infrequent or frequent intervals. Here we have to refer back to our statistics of drug administration which reveals that repetitious penicillin administration, in particular, four or more courses in 248 cases) retained its effectiveness in the great majority while the wide spectrum antibiotics (with a total of 485 courses of treatment) were applied either selectively as, for instance, in severe urinary and intestinal tract infections following sulfonamides or in obscure refractory cases of mixed infection where the desired response to the standard drugs, penicillin, sulfonamides, streptomycin, had proved disappointing. We are well aware of the variations in bacterial sensitivity to the whole array of antimicrobial agents and we have also encountered a number of clinically drug resistant infections, and this by the way not only among the staphylococcus group but also among streptococcus hemolyticus (but not viridans), although according to our experience complete therapeutic failures are strikingly fewer in number than the *in vitro* bacterial resistance studies would indicate. However, we intend to devote a separate study in the near future to this apparent absence of a parallelism between *in vivo* and *in vitro* microbial drug sensitivity.

This report on therapeutic results would evidently be incomplete without adding an account of mortality among these 872 cases. There were 39 deaths recorded. The causes were as follows: 10 leukemias, one Hodgkin's disease, one Wilms' tumor, one reticuloendotheliosis, one aplastic anemia, four fibrocystic diseases of the pancreas, four congenital heart lesions, three cases of congenital hydrocephalus, one subdural hematoma, one cerebellar tumor, two imperforate anus, one atresia of the bile duct, one intussusception, two pneumonias, one meningococcic meningitis, one tuberculous meningitis, one nephrosis, one pseudohermaphroditism with adrenal insufficiency, one ulcerative colitis, and one pulmonary moniliasis. In none of these cases, including the longstanding systemic monilia infection and the aplastic anemia could etiological connection be established between chemotherapy and the fatal outcome. However, the two pneumonia deaths, the meningococcic meningitis, and the ulcerative colitis, while admitted and readmitted in far advanced stages of the disease, must be classified as therapeutic failures.

Discussion

In the perennial struggle between pathogenic microbes and the human race the introduction of the aniline derivatives and of the mold derivatives have tipped the scale decidedly in favor of the human race.

As a desperate counter measure against the deadly molds the pathogenes have attempted a comeback through acquired resistance, possibly on the principle of survival of the fittest.

Yet large scale clinical experience still reveals day after day that a proper task force of antibiotic molds thrown into the battle without delay will route the bacterial enemy invader and save the day for the human host.

Only in rare instances will the molds, fighting on the side of men, turn traitor and cause serious harm to his traditional ally. In children such acts of allergic treachery on the part of the friendly molds occur still more infrequently than in adults.

After the first period of awe and enthusiasm over the antibiotic victories had somewhat dissipated, an attitude of critical assessment of gains and losses set in, and as so often is the case in political as well as in medical history, the pendulum has swung quite far to the other side. Numerous voices are being heard about the antibiotics being "security risks," ineffectual, stymying the natural immunological defenses, etc.

That is why a "do it yourself" and "look for yourself" attitude appeared to be the only sure way of arriving at valid conclusions about our past experiences and to formulate a rational therapeutic policy for the future.

SUMMARY

1. In a review of publications on antimicrobial therapy many divergent conclusions as to response to the available drugs are being pointed up. There is no consensus of opinion as to the occurrence and significance of (a) microbial sensitivity and resistance to drugs, (b) synergism, indifference or antagonism of drug combinations, (c) allergic or anaphylactic reactions of the human host.

2. The case histories of 872 patients who had received between three and 20 successive courses of antibiotic or chemotherapy at Milwaukee Children's Hospital within a 10 year period (3158 individual hospital admissions all told) were closely scrutinized and tabulated according to age, number of admissions, diagnoses and complications, type of drug administration, therapeutic response and allergic side effects.

3. The overall frequency of administration of the different drugs, which may be termed an antibiotic popularity contest, shows, as expected, penicillin way out in front with 2,892, followed by sulfonamides 909, streptomycin (given mostly in combination with penicillin) 555, followed by the several tetracycline preparations.

4. Lack of favorable clinical response to chemotherapy was hardly ever encountered although in cases with underlying severe systemic pathology like fibrocystic disease of pancreas, leukemia, congenital malformations, and possibly also agammaglobulinemia, etc., drug treatment could not accomplish more than temporary improvement, at times even after numerous exacerbations.

5. Penicillin, in particular, was administered in as many as 15 courses in one patient, in 248 cases four and more times. The clinical response in practically all cases was entered as partially or entirely favorable. Penicillin-streptomycin combination became a favorite routine in patients before specific bacteriological information was available. Sulfonamides and the tetracyclines were chosen mostly in urinary infections, then whenever bacteriological findings indicated preferential medication and finally in all cases refractory to the more popular drugs; most of these

belonged to the prognostically grave category of leukemias, fibrocystic disease and malformations.

6. In 72 cases of asthmatic bronchitis and bronchial asthma no untoward effects of repeated drug administration were noted. In 13 cases of allergic dermatitis 11 showed clearing in spite of repeated antibiotic therapy, only two developed erythema multiforme and roseola respectively without any threatening syndromes.

7. In 228 cases with major or minor surgery antimicrobial drugs were ordered more or less as a routine preoperative or postoperative procedure. In this policy all the attending members of our surgical staff in the different surgical specialties participated about equally. The results appear to have been most gratifying from the surgical as well as medical point of view.

8. There was a total of 39 fatalities out of 872 cases under review. None of them had even a remote causal connection with drug administration, except possibly two pneumonias in infants, one meningococcic meningitis and one ulcerative colitis, which cases might be classified as therapeutic failures. The rest of them were cases of hopeless prognosis like leukemia, congenital malformations, fibrocystic disease. In most of these cases repeated drug therapy was obviously instrumental in prolonging life.

9. On the basis of this varied and unselected material of hospitalized children it can be stated that the benefits of all the older and newer antimicrobial agents by far outweigh their shortcomings. We, therefore, consider it unwise to overemphasize the comparatively rare therapeutic failures and we do not hesitate to encourage the liberal use of these drugs, whenever indicated, by the younger generation of physicians who have never experienced the utter helplessness (except for immune body therapy) of the preantibiotic and prechemotherapeutic era.

RESUMEN

1. En una revisión de las publicaciones sobre terapia antimicrobiana, se señalan varias conclusiones divergentes en relación a la respuesta a las drogas con que contamos. No hay una igualdas de opinión en lo que se refiere a la frecuencia y significado de (a) sensivilidad microbiana y resistencia a las drogas, (b) sinergismo, antagonismo o indiferencia de las combinaciones de drogas y (c) reacción alérgica o anafiláctica en el huésped humano.

2. Las historias de los casos de 872 pacientes que han recibido entre tres y veinte series sucesivas de terapia por antibióticos o de quimioterapia durante un período de 10 años (3158 admisiones en total) en el Milwaukee Children's Hospital fueron escrutinizados atentamente y tabulados de acuerdo con su edad, número de admisiones, diagnóstico y complicaciones, tipo de droga administrada, respuesta a la terapéutica y efectos alérgicos colaterales.

3. La frecuencia total de la administración de las diferentes drogas, lo que podíamos llamar un concurso de popularidad de los antibióticos,

muestra, como era de esperarse, a la penicilina muy por delante con 2,892, seguida por las sulfonamidas con 909, estreptomicina (administrada generalmente en combinaciones con penicilina) 555, seguidas por las varias preparaciones de tetraciclina.

4. Casi nunca se encontró falta de respuesta clínica favorable a la quimioterapia a pesar de que en los casos con patología sistémica grave subexistente tales como enfermedad fibroquística del páncreas, leucemia, malformaciones congénitas y también posiblemente agamaglobulinemia, etc. el tratamiento medicamentoso no pudo lograr más que mejoría temporal, a veces aún después de numerosas exacerbaciones.

5. La penicilina en particular, fué administrada hasta en 15 series en un paciente y en 248 casos en cuatro o más veces. La respuesta clínica se consideró en todos los casos como parcial o enteramente favorable. La combinación de penicilina-estreptomicina vino a ser la rutina favorita en los pacientes en los cuales no se había obtenido información bacteriológica específica. Las sulfonamidas y las tetraciclinas fueron escogidas en su mayor parte en las infecciones urinarias, después siempre que los hallazgos bacteriológicos las indicaban como medicación preferente y finalmente en los casos refractarios a las drogas más populares, la mayor parte de los cuales pertenecían a la categoría de pronóstico grave como leucemias, enfermedad fibroquística y malformaciones.

6. En 72 casos de bronquitis asmática y de asma bronquial no se notaron efectos dañosos por la administración repetida de drogas. En trece casos de dermatitis alérgica, 11 mostraron limpieza a pesar de la terapia antibiótica repetida, sólo dos desarrollaron eritema múltiple y roseola respectivamente sin ningún síndrome alarmante.

7. En 228 casos con cirugía mayor o menor las drogas antimicrobianas fueron ordenadas más o menos como procedimiento de rutina pre y postoperatorio. Todos los miembros de nuestro grupo quirúrgico de las diferentes especialidades participaron aproximadamente igual de esta política. Los resultados parecen haber sido de lo más halagadores tanto desde el punto de vista quirúrgico como desde el médico.

8. Hubo un total de 39 muertes de nuestro total de 872 casos bajo revista. Ninguna de ellas tuvo ni la más remota relación causal con la administración de drogas, con la excepción posiblemente de dos neumonías en niños, una meningitis meningocóccica y una colitis ulcerativa los cuales se pueden considerar como fracasos de terapéutica. El resto de ellas eran casos de pronóstico desesperado, como leucemia, malformaciones congénitas y enfermedad fibroquística. En la mayor parte de estos casos la terapia repetida con drogas fué obviamente instrumento de la prolongación de su vida.

9. Teniendo como base este material variado y no seleccionado de niños hospitalizados, se puede afirmar que los beneficios de todos los agentes antimicrobianos tanto nuevos como antiguos sobrepasan en mucho a sus limitaciones. Consideramos por lo tanto, poco acertado el acentuar demasiado las fallas terapéuticas relativamente raras y no vacilamos en recomendar el uso liberal de estas drogas, cuando estén indicadas, por la

generación más joven de médicos que nunca han experimentado la impotencia (excepto por la terapia inmunológica) de la era preantibiótica y prequimioterápica.

RESUME

1. En surveillant la littérature sur la thérapie antimicrobienne on constate des conclusions fort divergeantes concernant les effets produits par les substances chimiques qui sont a notre disposition. On n'est pas d'accord (a) sur l'occurrence et la valeur de la sensibilité et la résistance microbienne, (b) le synergisme, l'indifference ou l'antagonisme des combinaisons chimiques, (c) les réactions allergiques ou anaphylactiques de l'organisme humain.

2. Les histoires de 872 malades qui ont reçue entre trois et vingt series de traitements antibiotiques ou chimothérapeutiques a L'Hôpital d'Enfants de Milwaukee au cours de dix ans (3158 admissions en tout) ont été examinés en détail et disposés en forme de tables suivant l'âge, nombre d'admissions, diagnostics et complications, choix de traitement spécifique, éffet du traitement, complications allergiques accessoires.

3. En éxaminant les quels parmis les differents médicaments ont été choisis le plus fréquemment—on pourrait parler de concours de popularité parmis les antibiotiques—on trouve sans doute la pénicilline fortement en premierè place (2892), suivie des sulfanilamides (909), streptomycine, surtout en combinaison avec la pénicilline (555), suivie par plusieures préparations de tetracycline.

4. L'éffet favorable de la chimothérapie, avec très peu d'exceptions, ne faisait jamais défaut. Quand mème, en cas de maladies graves systémiques comme la fibrocystique du pancréas, la leucémie, les malformations congénitales et possiblement l'agammaglobulinémie, etc., le traitement antimicrobien ne pouvait accomplir qu'une amélioration passante, parfois après des exacerbations nombreuses.

5. En un cas la pénicilline fut donnée autant que 15 fois à un malade, en 248 plus que quatre fois. Dans presque tous le cas l'éffet chimique fut recordé comme partiellement ou entièrement favorable. La combinaison pénicilline-streptomycine finissait par être le traitement préféré dans les cas ou il n'y avait pas encore d'information spécifique sur la bactériologie. Les sulfanamides et le tetracycline furent choisis particulièrement pour les infections urinaires, et puis aussi quant la détermination bactériologique demandait une médication spécifique, et surtout dans tout les cas où les médicines plus populaires manquaient de succès, généralement dans les cas de maladies graves comme les leucémies, les afflictions fibrocystics et les malformations.

6. En 72 cas de bronchite asthmatique et d'asthma bronchial les traitements fréquents ne produisaint pas d'effets des favorables. De 13 cas de dermatite allergique, 11 disparaissaient malgrès la chimothérapie répétée, et seulement deux dévelopaient l'une un érythème multiforme, l'autre la roséole, mais les deux sens syndromes menaçants.

7. En 228 cas avec chirurgie majeure ou mineure, les médicaments antimicrobiens étaient préscrits plus ou moins de manière d'une routine pré-

operative ou post-operative. Cette coutume etait adoptée par tous les membres du departement de chirurgie de l'hôpital, également par tous les differents specialistes. Il parait que les résultats étaient très satisfaisant du point de vue de chirurgie comme de médicine.

8. Il y avait 39 fatalitées parmi les 872 cas passés en revue. Pas une seule pouvait être attribuée mème de loin au traitement antimicrobien, excepté peut-être deux pneumonies d'enfance, une méningite méningococcique et une colite ulcérative, ces quatres cas devant peut-être être classifiés comme thérapeutique manquée. Les autres étaient des cas désespérés comme la leucémie, malformations congénitales, maladies fibrocystiques. Dans la plupart de ces cas le traitement antimicrobien répété évidemment avait le succès de prolonger la vie.

9. Selon cette matière clinique d'enfants hospitalisés, matière bien variée et surtout pas sélective, on peut affirmer que les substances antimicrobiennes, les plus vielles et les plus modernes, montraient bien plus d'avantages que de désavantages. Il paraît donc mal apropos d'accentuer trop fortement les défauts thérapeutiques assez rares, et nous n'hésitons pas d'encourager l'emploi libéral de ces substances antimicrobiennes, toutes les fois qu'il est indiqué, par les jeunes medicins qui n'ont jamais passé par l'experience d'impuissance complète de l'ère pré-antibiotique et pré-chimothérapeutique (excepté l'immunothérapie).

ZUSAMMENFASSUNG

1. In einer Literaturübersicht über die antimikrobielle Therapie werden hinsichtlich der Ansprechbarkeit auf die verfügbaren Medikamente viele unterschiedliche Schlussfolgerungen berichtet. Es bestehen Meinungsverschiedenheiten über Vorkommen und Bedeutung von (a) Keimempfindlichkeit und—resistenz gegenüber den Medikamenten; (b) Synergismus, Indifferenz oder Antagonismus von Arzneimittel — Kombinationen und (c) allergischen und anaphylaktischen Reaktionen des Menschen.

2. Die Krankheitsverläufe von 872 Patienten, die im Milwaukee Children's Hospital innerhalb von zehn Jahren zwischen drei und zwanzig Behandlungsperioden mit antibiotischer und Chemotherapie erhalten hatten (insgesamt handelte es sich um 3158 Krankenhauseinweisungen), wurden nach Alter, Zahl der Einweisungen, Diagnose und Komplikationen, Art der Arzneimittel-Verabreichung, dem therapeutischen Erfolg sowie nach den allergischen Nebenerscheinungen genau aufgeschlüsselt.

3. Einen Überblick über die Häufigkeit der Anwendung bereits bekannter antibiotischer Mittel zeigt—wie zu erwarten ist—dass das Penicillin mit 2892 an der Spitze liegt; dann folgen die Sulfonamide mit 909, das Streptomycin mit 555, das meist in Kombination mit Penicillin verabreicht wurde, weiterhin folgen die verschiedenen Tetracyclin-Präparate.

4. Ein Nichtansprechen auf die Chemotherapie wurde fast nie gefunden, es sei denn, dass in Fällen, denen eine schwere Systemerkrankung zu Grunde lag, ferner bei fibrocystischer Erkrankung, bei Leukämie, bei kongenitalen Missbildungen, vielleicht auch bei Agammaglobulinämie bei denen, die medikamentöse Behandlung nicht mehr als eine vorüberge-

hende Besserung erzielen konnte, zuweilen sogar nach zahlreichen Exazerbationen.

5. Insbesondere wurde Penicillin bei einem Patienten sogar fünfzehnmal angewandt und bei 248 Fällen viermal und mehr. Die klinische Ansprechbarkeit war praktisch in allen Fällen teilweise oder vollständig günstig. Die Kombination von Streptomycin und Penicillin erwies sich als Routine-Medikation auch bei Patienten, bei denen die bakteriologischen Resultate noch nicht vorlagen, als günstig. Sulfonamide und Tetracyclin waren bei Urogenital-Infektionen das Mittel der Wahl, sobald die bakteriologischen Ergebnisse ihre vorzugsweise Anwendung rechtfertigten, und schliesslich bei allen den Fällen, die auf die übliche Chemotherapie nicht ansprachen; die meisten davon gehörten zu den prognostisch ungünstigen Erkrankungen wie Leukämie, fibrocystische Erkrankungen und Missbidungen.

6. In 72 Fällen von asthmatischer Bronchitis und Bronchialasthma wurden keine ungünstigen Wirkungen durch wiederholte Chemotherapie gesehen. Von 13 Fällen mit allergischer Dermatitis zeigten 11 Reinigung trotz wiederholter antibiotischer Behandlung; nur in 2 Fällen entwickelten sich ein Erythema multiforme und Roseolen ohne bedrohliche Syndrome.

7. Bei 228 Fällen aus der grossen oder kleinen Chirurgie wurden Chemotherapeutika mehr oder weniger als Routine-Massnahme prae—oder postoperativ verabreicht. Diese Ansicht wurde von allen unseren Chirurgen der verschiedensten Fachrichtungen einmütig geteilt. Die Resultate waren sowohl vom chirurgischen als auch vom medizinischen Standpunkt aus höchst befriedigend.

8. Von unseren 872 beobachteten Fällen waren insgesamt 39 Misserfolge zu verzeichnen. Bei keinem von ihnen bestand ein Kausalzusammenhang mit der Chemotherapie mit Ausnahme vielleicht von swei Pneumonien bei Kindern, einer Meningokokkenmeningitis und einer ulcerierenden Colitis: Fälle, die als therapeutische Misserfolge zu verbuchen sind. Der Rest bestand aus Fällen mit hoffnungsloser Prognose wie Leukämie, kongenitale Missbildungen und fibrocystische Ergrankung. In den meisten dieser Fälle bewirkte die wiederholte Chemotherapie eine Lebensverlängerung.

9. Auf der Basis dieses verschiedenartigen und unausgewählten Krankengutes (Kinder) muss festgestellt werden, dass die Vorzüge der älteren und modernen Chemotherapeutika bei weitem ihre Mängel aufwiegen. Deswegen halten wir es für verkehrt, die relativ seltenen Misserfolge der Chemotherapie zu überwerten und zögern nicht, die freie Anwendung dieser Mittel bei entsprechender Indikation der jüngeren Ärztegeneration zu empfehlen, die niemals die äusserste Hilflosigkeit der vor-antibiotischen und vor-chemotherapeutischen Aera, in der nur die Immunkörper- Therapie zur Verfügung stand, erfahren hat.

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Bronchitis Circumscripta

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Bronchitis circumscripta is a localized circumscribed inflammation of the bronchial wall of unspecific nature. It belongs to those pathological patterns which we have learned to distinguish by means of accurate observation with the aid of modern diagnostic methods. But at the same time it belongs to those pathological patterns which keep us groping in the dark in search of their origin. Therefore, it is perhaps wise to presume that different causes may provoke the same phenomenon, and consequently it may be better to speak of the "bronchitis circumscripta-syndrome."

Medical literature is not rich in descriptions of this disease and the most important contributions came from European sources.

In 1938 it was Westermark,[1] who, in an article covering the whole subject of bronchostenosis, was presumably the first to describe cases of what we are now calling bronchitis circumscripta. However, he did not mention histological examinations.

Later, in 1944, Rist, Ameuille and Lemoine[2] published a paper about a condition which they called "Bronchite segmentaire." Lemoine and Leobardy[3] changed this name in 1949 to "Bronchite circonscrite," because in the meantime a better anatomic analysis had increased knowledge of lung segments. The symptoms of the disease which these French authors described are persistent cough, dyspnea or small hemoptyses. Diagnosis can be made only by systematic bronchoscopy. Thus they find a circumscribed inflammation of the bronchial wall. However, they demand as prerequisite, seeing through the bronchostenosis the distal, abrupt termination of the inflammatory process. Consequences resulting from the stenosis in the form of obstructive infiltration of the lung parenchyma behind the stenosis are not mentioned by these authors. In most of our cases, however, there was an obstructive infiltration or pneumonitis—nearly always wrongly called atelectasis in medical literature—behind the stenosis. This difference from the French authors probably results from their above mentioned prerequisite, for if it is necessary to see the distal end of the inflammation, the bronchostenosis is probably not narrow enough to cause an obstructive infiltration of the lung parenchyma.

There were more papers from Scandinavian authors. Leegaard[4] wrote in 1945 that he examined eight cases of what he called: "Bronchitis circumscripta non specifica." In his material he observed that distal to the bronchostenosis could occur symptoms of infiltration, pneumonia, abscess formation, etc.

In 1950 Hansen and Schmidt[5] communicated their observation of 25 cases of "Bronchostenosis of presumably unspecific inflammatory origin." They made a distribution in three stages: (1) local catarrhal, ulcerative or granulating inflammation without particular bronchostenosis; (2)

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bronchoconstriction with cicatricial retraction, and often manifestation of obstructive infiltration of the lung parenchyma; (3) inflammatory changes behind the stenosis chiefly of pneumonic character but also with bronchiectasis, abscess formation or empyema.

In the course of the last years we have observed in our department a series of 12 cases falling under the diagnosis of bronchitis circumscripta.

It is necessary to emphasize that both the clinical signs and the bronchoscopic image are distinctly different from the symptoms and phenomena of a pneumonic process with a secondary inflammation of the bronchial wall. Here the pneumonic signs with severe illness, high fever, etc., are paramount together with a more diffuse, less circumscribed inflammation of the bronchus. On the other hand in bronchitis circumscripta the clinical symptoms are usually much less severe, as one sees also in obstructive pneumonitis caused by neoplasma.

It appears to us that some examples of our series may illustrate the pattern of this pathologic entity better than an attempt to give an exhaustive description of all the phenomena that may occur in this disease.

We will also discuss some of the diagnostic difficulties which occur and the mistakes that must be avoided.

Case 1: A woman 37 years old underwent a strumectomy in 1953. Shortly after the operation she began to complain of dyspnea on exertion. A year later her complaints were so severe that she could hardly do her work.

On examination we found no infiltrations in the lung. The x-ray film of the chest showed a few calcifications in the left lung and thickened pleura with adhesions on the left side. Studies of the ventilatory function and analysis of the blood gases did not reveal a sufficient reason for her severe dyspnea. She had no heart disease. There was no stenosis of the trachea. Bronchoscopy revealed granulation tissue at the orificium of the left upper lobe bronchus. Distally of the granulation tissue the bronchial mucosa was normal. Histological examination of biopsy material from the granulation tissue showed unspecific inflammation. Smears from the bronchial secretion contained metaplastic squamous cells. Although no pathogenic bacteria were found in the sputum, she was given penicillin and streptomycin and after two weeks of treatment the granulation tissue in the orificium of the left upper lobe bronchus had completely disappeared and the bronchoscopic image was entirely normal. Also the dyspnea had disappeared for the most part. Her slight remaining dyspneic complaints now corresponded to the moderate impairment of pulmonary function caused by the pleural adhesions. The exact mechanism of the dyspnea caused by bronchitis circumscripta is not clearly understood.

Case 2: A boy 14 years old was hospitalized, in 1953, not in our department, with a shadow in the right lung. He did not feel ill. A definite diagnosis was not made at that time. The shadow disappeared spontaneously in the course of several weeks. Some months later the shadow in the right lung appeared to have returned, although the boy felt completely healthy. He was then sent to our department. He was a healthy looking boy with no complaints at all. The tuberculin reactions were negative. There was a shadow in the anterior segment of the right upper lobe. Bronchography showed a stop in the anterior segmental bronchus of the right upper lobe. Bronchoscopy revealed a swelling of the bronchial mucosa at the orificium of the right upper lobe bronchus, that was most manifest in the anterior segmental bronchus. Through the narrow stenosis of this segmental bronchus came pus containing hemolytic streptococci. There was also a localized area of granulation tissue in the right main bronchus opposite the orificium of the right upper lobe bronchus. Biopsy of this granulation tissue showed unspecific inflammation. He was treated with antibiotics (penicillin 1,000,000 E and streptomycin 1 gr. daily) during approximately four weeks. This resulted in complete disappearance of the granulation tissue and of the bronchostenosis. In the anterior segment of the right upper lobe remained a small fibrotic remainder of the obstructive pneumonitis. Until now (one year after his discharge from the hospital) no relapse has occurred.

Case 3: A woman 52 years old, came to our department when, by mass radiography, a shadow was found in the apex of the right lower lobe. She had no complaint. Lateral serial radiograms showed infiltration with multiple abscess formation in the apex of

the right lower lobe. By bronchographic and bronchoscopic examination a narrow stenosis of the apical segmental bronchus of the right lower lobe due to granulation tissue was demonstrated. Biopsy yielded unspecific inflammation tissue with cellular metaplasia. She was treated with penicillin and streptomycin parenterally and endobronchially (with the bronchus-catheter according to Métras[6]). But progression of the lesion developed, possibly due to the periodic local irritation by the bronchus-catheter. We then treated her only parenterally with antibiotics, and the granulation tissue disappeared completely. Two months later she was again hospitalized with the same symptoms as before. Repeated antibiotic treatment resulted once more in disappearance of the granulation tissue and the obstructive infiltration. In the apex of the right lower lobe remained a fibrotic residual of the infiltration. The cavities had disappeared. Until now (1½ years after discharge from the hospital) she has remained well.

Case 4: A woman of 42 was hospitalized with rheumatoid polyarthritis. During treatment she developed subfebrile temperature and complained of coughing with production of purulent sputum. On the radiogram she appeared to have a shadow in the apical segment of the right upper lobe. With bronchography a clearly localized stenosis at the beginning of the apical segmental bronchus of the right upper lobe could be demonstrated. Bronchoscopy showed a circumscribed swelling of the bronchial mucosa of the apical segmental bronchus of the upper lobe with longitudinal wrinkling. By histological examination of biopsy material and cytological examination of bronchial secretion, which contained no micro-organism, cellular metaplasia was demonstrated. Antibiotic treatment resulted in disappearance of all subjective symptoms. Bronchoscopic checking after treatment revealed only longitudinal wrinkling of the bronchial mucosa at the orificium of the apical segmental bronchus of the right upper lobe. This must be conceived as a symptom of cicatricial retraction. Subsequent bronchography showed a normal bronchial tree without demonstrable bronchostenosis. A relapse has until now (10 months after discharge from the hospital) not occurred.

The four cited examples are fairly representative for all our cases. A manifest feature is a nearly constant lack or poverty of subjective symptoms. Some of our patients were "victims of a mass radiography raid" (as we have come to express it) and were apparently completely healthy. Others had only minor complaints such as mild cough, small hemoptyses, subfebrile temperature or general feeling of slight discomfort. Only one complained of severe dyspnea on exertion.

Most of our cases had the radiographic findings of obstructive infiltration or pneumonitis, sometimes with bronchiectasis or abscess formation. Localized, circumscribed granulation tissue, sometimes with local longitudinal wrinkling of the bronchial mucosa was found in or near the orificia of a lobar or segmental bronchus. Bacteriological examination of the sputum and bronchial secretion was often negative or gave no clue as to the cause of the disease. Histological and cytological examination revealed unspecific inflammation often with cellular metaplasia.

Here we come to the essence of all diagnostic difficulties. Everyone acquainted with the art of cytology knows how difficult it can be to differentiate between cellular metaplasia and carcinomatous squamous cells, and everyone has made mistakes in this field.

There exists a kind of bronchiogenic carcinoma which we call "intramural carcinoma." It has a deeply infiltrating growth in the bronchial wall and the bronchial mucosa often has the same longitudinal wrinkling aspect which we encounter in bronchitis circumscripta. Moreover, biopsy taken during bronchoscopy sometimes yields no decisive results, since it is difficult to get sufficiently deep with the forceps. By cytological examination of sputum and bronchial secretion often only cellular metaplasia is found in these cases.

Although we are able to diagnose more than 97 per cent of our cases of bronchial carcinoma before thoracotomy, by histological or cytological

examination of material obtained by biopsy or punction or on smears of bronchial secretion or sputum, it is precisely these cases which gave us most difficulty in establishing diagnoses.

A short description of some case histories is again the best illustration of diagnostic difficulties.

Case 5: A man of 52 was hospitalized in 1949 with fever and complaints of coughing with production of blood-streaked sputum. These complaints began three weeks before admission to our department.

Physical and roentgenological examination revealed symptoms of obstructive pneumonitis in the left lower lobe. On bronchograms a circumscribed stenosis of the left lower lobe bronchus was seen. Through bronchoscopy we saw localized concentric narrowing of the left lower lobe bronchus with longitudinal wrinkling of the mucosa. Biopsy and cytological examination yielded cellular metaplasia. As we suspected intramural carcinoma, pneumectomy was performed. Histological examination of the operation specimen, however, revealed no tumor, but a carnification of the lobe distal to an unspecific localized stenosis.

Case 6: The history of this case seems nearly identical with that of Case 5. A man of 44 produced blood-streaked sputum two weeks before admission to the hospital. There appeared to exist an obstructive infiltration in the left lower lobe behind a circumscribed stenosis of the left lower lobe bronchus with longitudinal wrinkling of the mucosa. Distal to the stenosis normal bronchial mucosa was seen. Biopsy and cytological examination, however, revealed malignant cells. Thoracotomy was performed and an inoperable carcinoma was found.

Case 7: A man of 42 suffered, during two months before admission to the hospital, pain in his back and left side. A shadow in the left lower lobe was found and a circumscribed smooth stenosis of the left lower lobe bronchus was seen with bronchography and bronchoscopy. Behind the stenosis the bronchial tree and wall were normal. Biopsy and cytological examinations revealed no malignant cells. He was treated for bronchitis circumscripta, but a few weeks later he developed pleural exudate which contained carcinomatous cells. Later he was again hospitalized with cerebral metastases.

These examples clearly demonstrate how difficult the diagnosis can be and how easily mistakes can be made. Therefore it is of paramount importance that bronchoscopic biopsy and cytological examination be performed repeatedly before the diagnosis of bronchitis circumscripta can be made with reasonable certainty.

The possibility of bronchitis tuberculosa or perforation of a tuberculous lymph node into a bronchus must also be kept in mind. Sputum smears and cultures and biopsy of the granulation tissue or necrotic material will of course remove doubts in these cases.

SUMMARY

Bronchitis circumscripta is a pathological entity consisting of a localized, circumscribed ulcerative or granulating lesion of the bronchial wall usually situated in one of the orificia of a lobar or segmental bronchus. The inflammation may later manifest itself as a local cicatricial reaction.

Distal to the circumscribed bronchostenosis, obstructive infiltration sometimes resulting in pneumonitis, bronchiectasis or abscess formation may occur.

Subjective symptoms are often absent or slight. Examples of case histories are cited, and the difficulty of differentiating bronchitis circumscripta from a so-called intramural bronchiogenic carcinoma is stressed, particularly since histological and cytological examination may yield only cellular metaplasia in both diseases.

RESUMEN

La bronquitis circonscrita es una entidad patologica consistente en una lesión localizada, circunscrita, ulcerosa o granulosa de la pared bronquial

generalmente situada en los orificos de los bronquios segmentarios o lobares. La inflamación puede manifestarse más tarde como una reacción local cicatricial.

Distalmente a la broncoestenosis circunscrita hay infiltración obstructiva que algunas veces resulta en neumonitis, bronquiectasia o aún puede llegar a formarse un absceso.

Los síntomas a menudo faltan o son ligeros. Se citan ejemplos de historias clínicas y la dificultad para el diagnóstico diferencial con el llamado carcinoma bronquiogénico intramural se hace notar, especialmente en vista de que los exámenes citológico e histológico pueden dar sólo indicación de metaplasia celular en ambos padecimientos.

RESUME

La bronchite circonscrite est une entité pathologique consistant en une ulcération localisée, circonscrite ou présentant des granulations de la paroi bronchique, et habituellement située dans un des orifices d'une bronche lobaire ou segmentaire. Plus tard, l'inflammation peut se manifester comme une réaction cicatricielle locale.

En aval de la bronchostenose circonscrite une infiltration obstructive, résultant quelquefois en une pneumonie, des bronchiectasies ou la formation d'abcès peuvent apparaitre.

Les symptômes subjectifs sont souvent absents ou légers. Les auteurs présentent des exemples d'observations et insistent sur la difficulté de différencier la bronchite circonscrite du cancer bronchique dit intramural, surtout que l'examen histologique et cytologique peuvent ne montrer que de métaplasies cellulaires dans les deux affections.

ZUSAMMENFASSUNG

Die Bronchitis circumscripta ist eine pathologische Einheit, bestehend aus einer lokalisierten, umschriebenen, geschwürigen oder granulierenden Herdbildung der Bronchialwand, die gewöhnlich in einer der Öffnungen eines lobären oder segmentalen Bronchus liegt. Die Entzündung kann sich später manifestieren als eine örtliche narbige Reaktion.

Distal von der umschriebenen Bronchostenose kann eine Obstruktive Infiltration vorkommen die mitunter eine Pneumonitis, Bronchiektasie oder Abszessbildung zur Folge hat.

Subjektive Symptome fehlen oft oder sind gering. Beispiele von Krankengeschichten werden angeführt, und die Schwierigkeiten der Differenzierung der Bronchitis circumscripta vom sogenannten intramuralen bronchiogenen Carcinom werden betont, besonders nachem die histologische und cytologische Untersuchung bei beiden Krankheiten nur zelluläre Metaplasie liefern kann.

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Pneumothorax in Retrospect

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In recent years new concepts in the treatment of tuberculosis have appeared with increasing frequency. Effective antimicrobial drugs and new and improved surgical techniques are primarily responsible. One need not apologize, therefore, in admitting to a sense of confusion as regards therapy today, and for wishing for the days, not so long past, when the problem of how to care for patients with tuberculosis seemed simple by comparison.

Pneumothorax was for many years one of the most effective weapons against pulmonary tuberculosis. This can be attested to by thousands of rehabilitated persons today, including many physicians. It is difficult to understand the rapidity with which this therapeutic technique has been abandoned in this country. Many explanations for this have been advanced. We take issue in passing with only one of these: that a selective collapse by pneumothorax is "unphysiologic."

This report is an attempt to estimate, in cross section, what has been accomplished on the Tulane Pulmonary Disease Service, Charity Hospital, New Orleans, Louisiana, in years past when pneumothorax was used as the primary method of treatment. The results are not to be compared as a statistical evaluation of pneumothorax therapy with the reports of Mitchell.[1, 2, 3] More extensive and detailed information on the clinical evaluation of pneumothorax treatment has been published by Harris, et al,[4] and others.[5, 7, 8, 9, 12, 14, 17]

I. Material

The cases used in this report form a series in which satisfactory records were available, and in whom pneumothorax was the primary therapy. Most of these patients entered Charity Hospital in the years 1940-1945 and the initial pneumothorax was started while they were hospitalized. They have been followed in the Outpatient Department for varying lengths of time, as will be shown later. All patients were cared for by the Tulane Pulmonary Disease Service.

Since most of these patients began treatment during the years of World War II, the number of physicians on both the house and attending staffs was inadequate. Similar conditions existed in the Outpatient Department as regards clerical assistants and social service personnel, and the laboratories were limited as to the number of sputum examinations which could be handled. Due to frequent routine changes in the house staff on the Pulmonary Disease Service, the day-to-day information recorded in the progress and conference notes was not as complete as would be desired.

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For example, in very few cases could one determine the reasons for discontinuing pneumothorax therapy.

The fifty records evaluated represent 54 cases, since there were four instances of bilateral pneumothorax treatment included in this group.

II. Evaluation

Seventeen (31.5 per cent) of the 54 cases were males and 37 (68.5 per cent) were females. Thirty-six were married and 18 were single. Forty-eight (88.9 per cent) were white and only six (11.1 per cent) were colored. All of these colored patients were female.

TABLE I
AGE OF PATIENTS TREATED WITH PNEUMOTHORAX

Age	No. of Patients	Per Cent
5 - 14	2	3.7
15 - 24	23	42.6
25 - 34	8	14.8
35 and over	21	38.9
Total	54	100.0

The ages are shown in table I. It should be noted that 61.1 per cent of the cases were under 35 years of age when treatment was begun. This contrasts with the predominance of older patients coming under treatment today.

TABLE II
CLASSIFICATION OF DISEASE (N. T. A.)

Amount of Disease	Number of Patients	Per Cent	Unilateral Disease	Bilateral Disease
1. Minimal	3	5.5	3	0
2. Moderately Advanced	32	59.3	15	17
3. Far Advanced	19	35.2	4	15
Total	54	100.0	22	32

This table indicates the classification of the patient's original disease according to National Tuberculosis Association standards. Three (5.5 per cent) had minimal disease localized to one lung. Thirty-two (59.3 per cent) were classified as moderately advanced, with 15 having unilateral and 17 bilateral disease. In only four of these was disease confined to one lung.

The sputum was found to be positive before treatment was begun in 41 (75.9 per cent). Negative sputum reports were recorded for 12 (22.9 per cent). In one case the sputum had not been reported before pneumothorax was begun.

Pneumonolysis was attempted in 37 (68 per cent). In twenty-eight of these the operation was considered to be successful. There were nine failures to sever adhesions, but in seven of them the pneumothorax was continued.

Forty-eight (88 per cent) developed fluid on the treated side at some time during the treatment. In five of these, tuberculous empyema was proved. Spontaneous pneumothorax occurred twice, both on the side being treated.

TABLE III
DURATION OF PNEUMOTHORAX

Time in Months	No. of Patients	Per Cent
1 - 12	5	9.0
13 - 24	5	9.0
25 - 36	14	25.9
Over 36	30	56.1
Total	54	100.0

This table indicates the duration of pneumothorax treatment. Five (9 per cent) were maintained less than one year. Five (9 per cent) were discontinued in from 12 to 24 months after treatment was begun. Fourteen (25.9 per cent) were treated over a 24 to 36 month period. Thirty (56.1 per cent) were continued for more than three years. The longest period of treatment in this series was 10 years. Only seven were given antimicrobial drugs in conjunction with pneumothorax. Two received 15 grams of streptomycin, one 18 grams, three had 42 grams of streptomycin with PAS, and one has had 189 grams of streptomycin.

Thirteen (24 per cent) must be considered as pneumothorax failures. In three of them, pneumothorax was abandoned and some other form of treatment begun during the initial hospitalization. Two of these had thoracoplasty, and one received streptomycin, PAS, and pneumoperitoneum. Ten were readmitted to the hospital because of either: (1) presence of positive sputum or (2) x-ray evidence of reactivation or spread of disease. The shortest period before relapse in these 10 patients was four months, the longest 84 months after discharge. The average was 34.5 months. Some other form of active treatment was necessary in all 10.

The present status of these 54 cases is shown in table IV. Fifty (92.6 per cent) have been followed for more than three years and 34 of these, or 62.9 per cent of the total, have been followed for more than five years.

TABLE IV
PRESENT STATUS

Duration of Follow-up	Amount of Physical Activity: Modified Bed Rest (Home or Hospital)	4 Hours Work/Day	8 Hours Work/Day	Positive Sputum	Deaths
1. Less than one year 2 (3.7 per cent)	2	0	0	1	0
2. 1-3 years 2 (3.7 per cent	0	2	2	0	0
3. 3-5 years 16 (29.7 per cent)	1	0	15	0	0
4. Over 5 years 34 (62.9 per cent	2	3	29	0	0
Total Number	5 (9.2%)	5 (9.2%)	44 (81.4%)	1	0

The longest follow-up is 13 years. Five (9.2 per cent) remain on modified bed rest. Two of these are hospitalized at the present time, recovering from surgical treatment. Five (9.2 per cent) are working one-half day, presumably for a five-day week. Forty-four (81.4 per cent) are doing a full day's work either in the home or on the job.

Only one patient had a positive sputum recorded at the end of the follow-up period. This man is now hospitalized following lobectomy. It should be emphasized that these patients, most of whom are on an outpatient status, have not had frequent examinations of either sputum or gastric contents. Many of them deny raising sputum. Facilities for sputum collection and processing, and for doing gastric lavages in the outpatient clinics are not completely satisfactory as the amount of work the hospital laboratories can do is limited for the outpatient clinics.

There was no death in this series as of April 1, 1954.

III. Discussion

It has been accepted generally that the most suitable cases for pneumothorax are found in young individuals with minimal or moderately advanced disease localized in the apical or sub-apical portions of the upper lobes. The disease should be unilateral and of relatively brief duration, as determined by history and serial x-ray films. If these criteria are applied to the patients under discussion, it is clear that few of them were "good" candidates for pneumothorax therapy. This discrepancy emphasizes the conclusion that, at Charity Hospital in the years in which these patients were treated, we were confronted with a high percentage of patients with serious disease, and that our therapeutic choices were limited.

In the early and mid-1940's in New Orleans the beds available for patients with active tuberculosis were insufficient in number. Housing and living conditions were often substandard. Tuberculosis case finding, social service assistance, and public health nursing care were far below their present degree of effectiveness. The necessity for long periods on the waiting list before admission to the hospital in these years, more than anything else, is responsible for the low percentage of Negro patients coming under pneumothorax therapy. There were just not many of them suitable for such treatment by the time they were hospitalized. This is in spite of the fact that few of the 50 patients described above were good candidates.

The relapse rate and the necessity for re-treatment of 24 per cent of these cases is not surprising. It compares favorably with similar rates in series reported which contained a much higher percentage of minimal and unilateral disease in younger individuals. Perhaps the rate will rise somewhat with the passage of time. Perhaps analysis of a greater number of patients would produce a less promising figure, although one could scarcely select a more unsatisfactory group than the patients under discussion. With more careful follow-up studies, a higher percentage of transient x-ray changes and positive sputums would have been recorded, without much doubt. The fact that some humans never become cooperative is a factor here too.

It would be a waste of time to speculate on the results of treatment in these patients using the weapons and techniques now available. Likewise, it would prove nothing really, to compare this group with patients having similar amounts of disease under treatment today. The patients and the conditions under which they lived and contracted their disease would be different.

If one considers the amount, extent, and duration of the disease in these patients at the beginning of treatment and the facts that: (1) 81.4 per cent of them are leading normal existence again and (2) none of them died of tuberculosis, the over-all results of treatment in this group must be considered satisfactory. This is especially true in a disease characterized by chronicity, systemic distribution, and a natural tendency to relapse.

SUMMARY

An analysis of 54 cases successfully treated primarily by pneumothorax while in the hospital, is presented. The reasons for the lack of complete follow-up information are discussed. The handicaps in the proper treatment of patients with extensive tuberculosis in New Orleans, Louisiana, in the period from 1940 to the advent of streptomycin are stressed. The conclusion is reached that the over-all results of treatment in this group: 81.4 per cent returned to full activity with no deaths, are satisfactory; a good initial result with pneumothorax in a suitable case will, in the great majority of instances, result in an excellent control over the patient's disease.

RESUMEN

Se presenta un estudio de 54 casos tratados desde luego con neumotórax en este hospital. Se discuten las causas para la falta de siguimiento de estos enfermos. Las desventajas para el tratamiento adecuado de los enfermos con tuberculosis avanzada en New Orleans, Louisiana, en el período desde 1940 hasta el advenimiento de la estreptomicina, se hacen notar. Se llega a la conclusión de que el resultado en total a que se llegó fué como sigue: 81.4 por ciento volvieron a completa actividad sin que ocurrieran entre ellos defunciones y son satisfactorios. Un buen resultado inicial de neumotórax en un caso adecuado en la mayoría de los casos, resulta en un dominio excelente del padecimiento más tarde.

RESUME

Les auteurs présentent l'analyse de 54 cas traités à l'hôpital d'emblée par pneumothorax, et ayant donné de bons résultats. Ils discutent les raisons qui les empêchèrent d'obtenir des examens de contrôle complets. Ils insistent sur les aléas du traitement que subissaient les malades atteints de tuberculose extensive à New-Orléans (Louisiane) pendant la période qui s'étend de 1940 jusqu'à l'apparition de la streptomycine.

Ils arrivent à la conclusion que l'ensemble des résultats du traitement sont satisfaisants (81,4% des malades retournèrent à leur activité normale, aucun décès). Un bon résultat au début, associé à un pneumothorax quand il est indiqué, permettra dans un grand nombre de cas, de venir parfaietment à bout de la maladie.

ZUSAMMENFASSUNG

Eine Analyse von 54 im hiesigen Krankenhaus erfolgreich in erster Linie mit Pneumothorax behandelten Fällen wird vorgelegt. Die Gründe für das Fehlen vollständiger Informationen über der späteren Verlauf werden besprochen. Die Schwierigkeiten bei der geeigneten Behandlung von Kranken mit ausgedehnter Tuberkulose in New Orleans, Louisiana während des Zeitraumes von 1940 bis zum Aufkommen des Streptomycins werden betont. Man gelangt zu dem Schluss, dass die Gesamtergebnisse der Behandlung in dieser Gruppe: 81,4% kehrten zu ihrer vollen Tätigkeit zurück ohne Todesfälle, befriedigend sind; ein in einem geeigneten Fall mit Pneumothorax erzieltes gutes Anfangsergebnis wird in der grossen Mehrzahl der Fälle mit einer ausgezeichneten Behrrschung der Erkrankung des Patienten enden.

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Congenital Diaphragmatic Hernia with Malrotation of the Liver

A Case Report

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Diaphragmatic hernias due to embryological deficiencies of the diaphragm are usually of three main types: (1) those through the pleuroperitoneal hiatus, (2) those due to the lack of formation of the posterior portion of the diaphragm and (3) those through the foramen of Morgagni (Larrey's spaces). In a series of 430 diaphragmatic hernias of all types reported by Harrington only nine were due to a congenital defect of the pleuroperitoneal hiatus. In our patient the defect was in the pleuroperitoneal hiatus, and presented two interesting findings: it occurred on the right side and was associated with an unusual displacement of the liver and gall bladder.

Case Report

R. McK. (W. T. T. H. 2939) a 30 year old, colored male was admitted to the hospital on August 25, 1953 with a tentative diagnosis of tuberculous pleural effusion. He was completely asymptomatic at the time of admission but had an exposure history to a brother previously treated for tuberculosis. Fifteen years prior to this admission he had undergone operation for correction of congenital club foot in another hospital. The remainder of the history was noncontributory.

Physical examination revealed a poorly developed, moderately well nourished, colored male of about the stated age. The pertinent physical findings were limited to the extremities and chest. A congenital deformity of the right hand and forearm as well as the residual deformity of a congenital club foot were present. Examination of the chest revealed limited expansion of the right hemithorax and a decrease in breath sounds along the base of the right lung posteriorly. The heart was also displaced to the left on percussion.

Hematology studies pre-operatively showed a red cell count of 5.79 millon, white cells 6,350, hemoglobin 15.65 grams and normal differential smear. Urinalysis was normal. Eight sputum examinations were negative to both concentrate and culture for tuberculous organisms. Skin tests were negative for tuberculosis and blood chemistries were within normal limits.

Roentgenograms in the postero-anterior and lateral positions showed a haziness of the lower one-half of the right lung field. The heart was displaced slightly to the left. Barium studies were done on the intestinal tract and revealed the complete displacement of the jejunum, ileum, ascending colon and proximal half of the transverse colon within the right hemithorax (Figures 1 and 2).

The patient was explored on November 30, 1953 using a combined thoraco-abdominal approach through the eighth intercostal space under endotracheal cyclopropane-ether-oxygen anesthesia. The liver was found to be rotated into the left upper quadrant so that the gallbladder was in the posterior position. The defect in the diaphragm was in the region of the pleuro-peritoneal hiatus with herniation of the entire small bowel and right colon almost to the splenic flexure, into the right hemithorax. There was a marked compression of the lower and middle lobes of the right lung. Adhesions between the loops of bowel were dissected free with a minimum amount of difficulty. It was necessary to divide the intact portion of the diaphragm down to the area of the defect before the intestinal tract could be returned to the abdomen. The defect was repaired by overlapping the posterior portions over the anterior with interrupted black

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silk sutures. The liver was then rotated back to a more normal position in the right upper quadrant although the gallbladder still remained posteriorly. Decortication of the thickened pleura over the right lung was done. The lung expanded fairly well and the pleural cavity was drained by two thoracotomy tubes connected to a suction apparatus. The abdominal and thoracic incisions were then closed in layers.

Post-operatively he had delayed expansion of the right middle and lower lobes which eventually responded to aspiration and tube drainage. A moderate degree of gastric retention was also present immediately after the operation, requiring intestinal intubation with Levine and Miller-Abbott tubes, bland diet and antispasmotics. These complications responded to conservative treatment, however, over a period of two weeks. A cholecystogram was done just prior to discharge and revealed the gall bladder to be located superior and posterior to its normal position. However, there was good visualization and excellent emptying after fatty meal (Figure 2). The patient was discharged January 3, 1954.

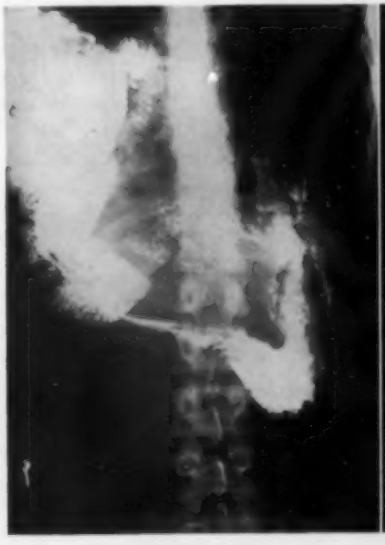

FIGURE 1

FIGURE 2

Figure 1: Upper G. I. Series showing displacement of the duodenum, jejunum and ileum into the right hemithorax.—*Figure 2:* Post-operative cholecystogram: Arrows point to gallbladder located posteriorly and superiorly.

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Chemotherapy of Cancer in the Teaching of Diseases of the Chest*

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The rapidly rising incidence of bronchogenic carcinoma in the last two decades has affected not only the chest specialist; it has already had a profound effect upon the whole approach to diseases of the chest in our medical schools. In the past, chest disease meant primarily tuberculosis with other abnormalities considered largely in terms of differential diagnosis. The great majority of cases of chest disease that the medical student and internist saw were of tuberculous etiology, and tuberculosis was inclined to dominate his thinking on the subject of chest disease thereafter. Today, on the other hand, cases of bronchogenic carcinoma outnumber new cases of tuberculosis in some chest services.

In certain respects this has stimulated increasing interest in chest diseases. Diagnosis has become again a significant medical problem because of the protean manifestations of lung cancer. Thoracic physiology bears a more obvious relationship to disease processes since many of the manifestations of lung cancer, such as atelectasis, are the result of disturbance to normal function. At the same time, the rise in lung cancer rates has had a distributing effect upon the teaching of chest disease, because diagnosis tends to be regarded as the end of the problem. Those patients who are operable are referred to surgery; the rest, being incurable, may benefit from radiation therapy, also a matter for experts, but, by and large, little can be done for them. By such reasoning a student may consider diagnosis of limited significance.

There is little doubt that chemotherapy will be increasingly used in treating cancer of the lung in the next few years, even if there is no spectacular improvement in drugs and techniques. The benefits for most patients are already substantial. There is some hazard in these procedures, but they are not so complicated that specialists are required, and certainly cancer chemotherapy will be undertaken by internists and general practitioners on an increasingly greater scale in the next few years. There is everything in favor of teaching such chemotherapy in medical schools.

The amount of new information required is relatively small. The common agents are those already used for malignant disease of the hematopoietic and reticuloendothelial systems. Administration is much the same, and limitations are the same. The problem of husbanding chemotherapeutic resources against the factor of decreasing effectiveness is also the same,

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*The Tenth in a New Series of Articles Prepared under the Sponsorship of the Council on Undergraduate Education of the American College of Chest Physicians.

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although the problem of invasion of neurological and vascular structures adds a further dimension to chemotherapy of bronchogenic carcinoma. But it still does not constitute an entirely new subject; it is only an extension of a form of chemotherapy already in the curriculum.

At the same time cancer chemotherapy offers a dramatic representation of the significance of pulmonary anatomy and physiology. The relief of obstructive emphysema and atelectasis are dynamic aids in the teaching of bronchial anatomy and pathology. The systemic therapy of malignant effusions resulting from a centrally located mass producing lymphatic blockade, as distinguished from the intracavitary approach to effusions due to pleural metastases, demonstrate the clinical importance of the role of lymphatics in pulmonary disease. The dramatic response of the superior vena caval syndrome to chemotherapy, the fact that intravenously administered agents results in direct intrapulmonary artery distribution, and the important relationship of the bronchial artery supply to pulmonary lesions contribute to a better appreciation of circulatory aspects of pulmonary disease. Clearly, experience with cancer chemotherapy can result in a practical working understanding of thoracic physiology of great value in all phases of chest medicine.

But most important of all, the inclusion of cancer chemotherapy in our curricula will prevent any feeling of hopelessness about this division of chest diseases. It will give point to diagnostic efforts if the student realizes that useful, even if not curative, treatment will follow. The differential diagnosis between a primary and metastatic lesion assumes additional importance if it affects treatment, and the student must feel that some form of treatment is available for at least the majority of patients. If we are to make the best of a difficult situation every doctor must have a real interest in the subject of lung cancer diagnosis and treatment, and this can only be accomplished in our medical schools.

The President's Page

As my term of office as President of the College nears its completion, I would like to express my appreciation to all of the officers and to the members of the councils and committees for their fine cooperation. From the reports I have received, it is apparent that the College councils and committees have been engaged in carrying forward constructive and interesting programs. Many of these councils and committees will present reports at the 22nd Annual Meeting in Chicago, June 7-10, 1956.

It is difficult to evaluate the progress and accomplishments made during the term of office of a president, especially when one considers that work does not begin when a president is elected nor terminate at the end of his tenure. The college program is a continuing chain of well-planned activities which are carried on year after year. A president of the College can assist this program by injecting his enthusiasm into the many activities planned by the Board of Regents and carried out by the various councils and committees. It has been my aim as president of the College to assist in maintaining the high ideals of the society.

During the past 22 years, the College has evolved from the infant stage to its present position as a leader among medical specialty societies. What the College has accomplished during the past year is directly proportional to the enthusiasm displayed by its members and I would therefore like to extend to them my sincere and heartfelt thanks for their full measure of cooperation.

The world in which we live is geared to a fast pace. To keep up, rather than be left by the wayside, our College must be alert to the changing times. This is a challenge which your elected officials have met successfully over the years. I am indeed happy to report that the American College of Chest Physicians has assumed the attitude of careful planning and the strict adherence to our high aims and objectives. In all our endeavors, the College holds one objective uppermost—how may we better serve our members? On my many visits to the College headquarters, this principle has been evident.

The scientific and social program for the 22nd Annual Meeting of the College, the various postgraduate courses on chest diseases, the College journal, *Diseases of the Chest*, the numerous books published and in the process of being published by the College, and other activities indicate a sincere desire to better serve the members. The membership activities during the past year have been successful in the sense that men of high quality and training were admitted to the College. This has been true ever since the College began and will, I am sure, continue in the future.

I am heartened and pleased that so large a number of College members serve on our important councils and committees. These groups provide an opportunity for service and the splendid results achieved by them are of tremendous value, not only to members of the College throughout the world, but to physicians in general. Their reports, many of which have been published in *Diseases of the Chest* and in other journals, are most stimulating. A great deal of effort has gone into the planning and execution of these reports. Again, this is an indication of our desire to serve the membership, and in return, have the members serve the College. Service in any organization is a two-way street and the College is no exception.

I would particularly like to pay my compliments to the faithful members of the staff at the Executive Offices of the College in Chicago whose splendid cooperation has made my term of office so enjoyable.

I would like to close this message by expressing my sincere appreciation for your confidence and trust in electing me to the office of president. Mrs. Stygall and I are looking forward with much pleasure to greeting all of you at the College meeting in Chicago next month.

James H. Stygall

22nd ANNUAL MEETING

Next month the College will celebrate its 22nd Annual Meeting in Chicago, Illinois. The Hotel Sherman will be headquarters for the meeting, June 7 through 10. During the following week, June 11 through 15, The American Medical Association will hold its 105th Annual Meeting, and many of our members will want to remain in Chicago to attend the sessions of the Section on Diseases of the Chest, as well as visit the splendid scientific and technical exhibits.

Copies of the very fine scientific program for the College meeting have been forwarded to members in Canada, the United States and its possessions. An *Advance Registration Form* and *order form* for the Seminars, Round Table and College Conference Luncheons, and the Presidents' Banquet are contained in the program. These forms are now being received at the Executive Offices of the College in large numbers, which indicates that it will be a very well attended meeting. College members and other interested physicians are urged to send in their Advance Registration and order forms as soon as possible so that their badges, tickets, program and other material may be prepared and awaiting them upon arrival. Copies of the program may be obtained by writing the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois.

The ladies program for the 22nd Annual Meeting includes a luncheon and puppet opera at the Kungsholm Scandinavian Restaurant and a theater party to see "*Oklahoma,*" the new Rodgers and Hammerstein's great musical spectacular. Both of these functions will take place on Friday, June 8, and reservations must be made in advance.

On Sunday, June 10, the closing day of the meeting, a cocktail party will be held at the College Building at 112 East Chestnut Street, just a few minutes' trip by taxi from the Hotel Sherman. This will give many members who have not visited the Executive Offices an opportunity to see the beautiful and modern headquarters of the College.

Please write directly to the Hotel Sherman for your reservations and don't delay—it's the *Meeting of the Year!*

REPORT OF THE COMMITTEE ON INDIAN AFFAIRS

The Committee on Indian Affairs of the American College of Chest Physicians announced that a study is now being conducted by the Bureau of Indian Affairs, U. S. Public Health Service, and the Henry Phipps Institute of the University of Pennsylvania to determine if prophylaxis and/or cure of early tuberculosis infection is feasible through chemical agents or drugs.

Under the Field Directorship of Dr. Arthur W. Dahlstrom, Chairman of the College Committee on Indian Affairs, this study will determine the effect of using one or more of the anti-tuberculosis drugs such as isoniazid in:

a) preventing the progression of infection in children
b) reverting tuberculin reactors to tuberculin-negative sensitivity
c) preventing the development of tuberculin sensitivity among a general child population of negative reactors.

The Phipps Institute will carry out this program among the United Pueblos, Consolidated Utes, Jicarilla Apaches, Mascalero Apaches, and possibly other Indian groups.

All reports published by the Phipps Institute of the University of Pennsylvania shall indicate the role of the Public Health Service in the project and likewise give recognition to the original study proposal submitted by the Committee on Indian Affairs of the American College of Chest Physicians to the Commissioner, Bureau of Indian Affairs. Papers on clinical application of the study will first be offered for publication to *Diseases of the Chest.*

It is contemplated that the study will require a minimum of three years.

The Committee on Indian Affairs of the American College of Chest Physicians wishes to express its appreciation for the interest and cooperation shown by the Henry Phipps Institute of the University of Pennsylvania and the appropriate bureaus of the Public Health Service in making this important study possible.

Carl H. Gellenthien, M.D., Vice-Chairman
Committee on Indian Affairs

College News Notes

Dr. J. Ivan Hershey, Bryn Mawr, Pennsylvania, has recently been appointed Chief of Medicine by the Veterans Administration for their hospital in Marlin, Texas.

Dr. Edward Dunner, Washington, D. C., formerly Chief of Training and Standards, Tuberculosis Service, Veterans Administration, has been appointed Secretary of the Committee on the Chemotherapy of Tuberculosis of the Veterans Administration.

Deputy Army Surgeon General James P. Cooney's promotion to Major General was confirmed by the United States Senate on March 16, 1956. He had received an interim promotion to that rank on September 16, 1955. General Cooney was sworn in as the Deputy Surgeon General of the Army on July 13, 1955 when he succeeded Major General Silas B. Hays who had become The Surgeon General of the Army on June 1. General Cooney has achieved distinction as one of the Army's outstanding authorities on radiology and the medical effects of atomic explosion. In 1946, he was assigned to the Manhattan Engineering District to train for the Bikini tests where he served as the representative of the Army Surgeon General and participated in numerous radiological surveys. After Bikini, he was sent on a special mission to Japan to study the A-bomb surviors at Hiroshima and Nagasaki. General Cooney is a member of the Board of Governors of the College.

Dr. Seymour M. Farber, San Francisco, has recently been appointed Head of Medical Extension at the University of California Medical Center.

Dr. Burgess L. Gordon, Philadelphia, Pennsylvania, **Dr. Aldo Luisada,** Chicago, Illinois, **Dr. Emil Rothstein,** Brockton, Massachusetts, **Dr. B. B. Bagby, Jr.,** Oteen, North Carolina and **Dr. Samuel Phillips,** Memphis, Tennessee, recently lectured at the Veterans Administration Hospital, Memphis, Tennessee. **Dr. P. J. Sparer,** Memphis, was program director for the lecture series on "Psychiatry, Psychosomatics, and Tuberculosis."

College Chapter News

QUEBEC CHAPTER

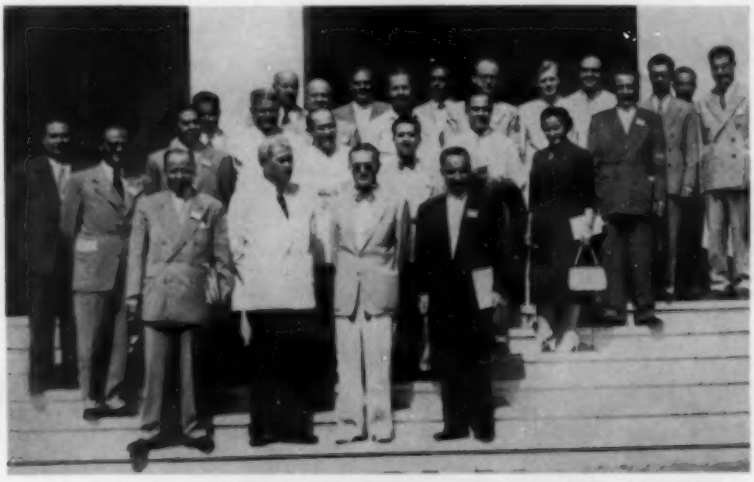
The Quebec Chapter of the College met jointly with the Societe de Phthisiologie at the Institut Bruchesi, Montreal on January 13. The problem of tuberculosis was discussed by the following: Drs. J. A. Vidal, Raymond Boisvert, B. Guy Begin, and J. Paris.

MIDDLE EAST CHAPTER

The 1st annual meeting of the Middle East Chapter was held recently in Bhamdoun, Lebanon under the auspices of the Minister of Health. Dr. Philip Chedid, President of the Order of Physicians in Lebanon, gave the opening address which was followed by an address by Dr. Elias Khoury. Dr. Papken S. Mugrditchian, Governor for the College, welcomed members and guests. Representatives from Lebanon, Syria, Iraq, Saudi-Arabia, Kuwait, Bahrein, and Cypress attended the meeting. The following officers for 1956 were elected:

President:	Cesar Chehab, Beirut, Lebanon
Vice-President:	Ahmed Salameh, Kuwait, Kuwait
Secretary-Treasurer:	Wagih K. Sabbagh, Biet Mery, Lebanon

The second annual meeting of the chapter will be held at the Ambassador Hotel, Bhamdoun, Lebanon, August 10-12, 1956.



The First Meeting, Middle East Chapter, Bhamdoun, Lebanon, September 16-18, 1955. First row, left to right; Cesar Chehab, Elias Khoury, Joseph J. McDonald, and Papken S. Mugrditchian.

PERUVIAN CHAPTER

The 9th annual meeting of the Peruvian Chapter was held in Lima, February 29, March 1 and 2 at the Dispensario Central Antituberculoso "Max Arias Schereiber." A scientific program dealing with cardiovascular and pulmonary problems was presented. The following officers were elected:

President:	Victor Narvaez, Lima
Vice-President:	Mario Pastor, Lima
Secretary:	Jose Almandoz Veliz, Lima
Treasurer:	Alejandro Flores, Lima

GERMAN MEDICAL JOURNAL*

In January, 1956, the first issue of *German Medical Journal*, a monthly English language edition of *Deutsche Medizinische Wochenschrift*, appeared. This journal, which is now in its 81st year, is the leading weekly medical journal of German-speaking countries. It has long been known to contain a large volume of valuable material. However, this has not been available to physicians in various parts of the world because of language deficiency. Therefore there have been numerous requests from physicians from many parts of the world for an English edition of *Deutsche Medizinische Wochenschrift*.

This English language edition, which is already appearing monthly, contains the most important articles from the weekly journal, and in order to provide a general picture of German medical science and practice, it carries editorials, abstracts, reviews, scientific briefs, questions and answers, as well as medical news and views from German medical clinics and research institutes. A considerable amount of this material is being written especially for the *German Medical Journal.*

Language deficiencies have always been a great handicap to peoples of the world with scientists and physicians as no exception. Many journals have attempted to bridge the gap by publishing a summary of each article in two or more languages. Certainly no journal with even small international distribution should do less. "It is the purpose and aim of the *German Medical Journal* to establish and maintain a close relationship between English speaking doctors in other countries and their colleagues in German medical clinics, institutes and practice. In this way the exchange of medical research and practical experiences will be greatly facilitated and thus promote the further development of international medicine." This is a most laudable undertaking and one which should be supported by English speaking physicians everywhere.

J. Arthur Myers, M.D.

*Published by Georg Thieme Verlag, Stuttgart, Germany.

BOOK REVIEWS

CANCER OF THE LUNG, by Milton B. Rosenblatt and James R. Lisa. Published by Oxford University Press, New York, 1956, 330 pages. Price $15.00.

The book presents a very interesting historical review of the development of knowledge concerning carcinoma of the lung. It is pointed out that the increase in incidence of the disease is global in distribution. The various possible factors that play a role in the increased incidence of the disease and influence its course are discussed. The authors are of the opinion that cigaret smoking is not an important factor in the causation of carcinoma of the lung.

The difficulties involved in early diagnosis of carcinoma of the lung are discussed, and the various diagnostic aids that are available to establish the diagnosis are presented. The importance of physical and roentgen examination of the thorax, of cytologic study of sputum and bronchial secretion, and of bronchoscopy is reviewed. Unfortunately, as pointed out, there still exists a difference of opinion among pathologists as to the terminology that should be employed in classifying the various types of carcinoma of the lung. The problem of differential diagnosis of adenoma of the bronchus and carcinoma is touched upon.

An excellent discussion of the surgical treatment of carcinoma of the lung is presented without going into the finer technical details. Unfortunately, one gains the impression in reading the book that the authors have a very pessimistic attitude—that very little likelihood exists that much progress will be made in earlier diagnosis of the disease. This is especially reflected in the chapter on physical diagnosis. Consequently, according to this impression the prospects of improving the survival rates by surgical removal of the tumor are gloomy.

Herman J. Moersch, M.D.

YOUR BLOOD PRESSURE AND HOW TO LIVE WITH IT, by William A. Brams. Published by J. B. Lippincott Company, Philadelphia, Pennsylvania, 1956. Price $2.95.

This is the second book on heart disease Dr. Brams has written for the lay person. Dr. Brams, Associate Professor of Medicine Emeritus at the Northwestern University Medical School and Senior Attending Physician at the Michael Reese Hospital in Chicago, had already written a very successful book on "Managing Your Coronary."

Dr. Brams devotes chapters on advances in treatment, the life span and the symptoms of high blood pressure. He advises the patient to see a doctor, not to take his own advice or that of his friends, or the taxicab driver, or the grocer. He has chapters which include weight charts, reducing diets, a list of rehabilitation agencies.

The book is readable. It is written in simple clear English and only rarely would the lay person be in doubt as to the meaning. It is an optimistic book. The author avoids giving actual figures on what constitutes hypertension and perhaps he is wise to do this. He cites interesting case histories which will undoubtedly be reassuring to the lay person and will be an aid to the doctor who wishes to suggest reading matter to his patient. The book can be recommended to patients. However, the American Heart Association and local Heart Associations have recently been publishing excellent brochures that are "give-aways," or sell very cheaply. Dr. Brams' book will really have competition now whereas a few years ago, it would have had great success.

Arthur M. Master, M.D.

RECENT ADVANCES IN RADIOLOGY, by Thomas Lodge. 3rd Edition, Little, Brown and Company, Boston, Massachusetts. 358 pages, Price $10.00.

As stated in the preface to this third edition, "It has been thought advisable herein to refer to work which is not strictly recent but which has an essential place in the development of current radiological thought." Therefore, this edition presents a review of general hospital problems, and only briefly alludes to many of the new radiological methods and machines. Such recent advances as spot film radiography, high voltage techniques, fluoroscopic intensifiers, and rapid serial radiography are not mentioned. The clinical entities are selected according to the authors' interests, and though dealt with concisely and orderly, they are not all inclusive. For example, the problems of gastric neoplasm and the ulcer cancer relationship are presented, while no mention is made of duodenal ulcer disease. There are brief references to many of the modern concepts of disease etiology with mention of their proponents. The format is pleasing and at the end of each section, numerous references are listed.

Lloyd Mark, M.D.

Obituary

ARTHUR M. WALKER
1896 – 1955

(Veterans Administration photo)

The untimely death of Arthur M. Walker shocked workers in diseases of the chest everywhere. His previous fine contributions, his present work, and his vision of future accomplishments had set the stage for greater achievements which were being anticipated by the medical profession.

He was born in Pittsfield, Massachusetts, September 26, 1896. He attended Chicago Latin School, Chicago, Illinois, Westminster School, Simsbury, Connecticut, Williams College, Williamstown, Massachusetts and Harvard Medical School, Boston.

Entering the Army, World War I, in August, 1917, he fought valiantly and received wounds in August and September, 1918. In October of that year he was commissioned captain and two months later, invalided to the United States. He was decorated with Purple Heart with Oak Leaf Cluster.

He re-entered Williams College and graduated with his class, receiving the Bachelor of Arts degree, Maxima Cum Laude, in 1919. In two and one-half years, he completed the regular four-year college course and was elected member, Phi Beta Kappa. When he graduated from Harvard Medical School in 1923, he was top man in his class and had been elected to Alpha Omega Alpha. Following a

two-year internship at Massachusetts General Hospital, he was appointed instructor in pharmacology at the University of Pennsylvania. In due time, he was promoted in rank and served as Associate Professor from 1938 to 1941. The next year he was assistant to the chairman of the Committee on Medical Research, Office of Scientific Research Development, Washington, D. C. As Lieutenant Colonel, he was registrar and "drill master," 20th General Hospital (University of Pennsylvania), Louisiana, Burma, India, in 1942 and 1943, and the next two years, Combat Liaison Officer with Stillwell's Chinese Troops in Burma. He then spent approximately four months as historian, Committee on Medical Research, Office of Scientific and Research Development, Washington, D. C.

Dr. Walker contributed chapters on "Antimalarials," "Blood and Blood Substitutes," "Penicillin," and "Insecticides and Rodenticides" to *Scientists Against Time*, published in 1946. The next year this book was awarded the Pulitzer Prize in History.

Dr. Walker's first contact with antibiotics was during the development of penicillin as assistant to Dr. A. N. Richards in the Committee on Medical Research, Office of Scientific and Research Development. It was from those experiences that he wrote what is still the classical chapter in *Scientists Against Time*. This prepared him admirably for the important positions he held during the last decade of his life. A. N. Richards, when he was President of the National Academy of Sciences, stated that Walker's magnum opus was his development of methods and skills for the study of urine formation in the opaque mammalian kidney which had hitherto been applicable only to the transluscent amphibian kidney.

Dr. John Barnwell had just become Director of Tuberculosis of the United States Veterans Administration in 1946 and saw not only the need of, but also the opportunities for extensive study of antibiotics and other chemotherapeutic agents in tuberculosis. The same year he was able to induce Dr. Walker to accept the position as Director of Chemotherapy in his tuberculosis service. In 1950, Dr. Walker was promoted to the chiefship of Research and Education on this same service. Throughout this 10-year period, Dr. Walker led the Veterans Administration-Army-Navy Cooperative Studies in the Chemotherapy of Tuberculosis, as secretary of the Executive Committee. He was editor of Veterans Administration Technical Bulletins Series 10 on various medical subjects, which has been widely hailed throughout the world by medical editors and educators, having reached a circulation of 13,000. He also sent out a series of mimeographed quarterly reports which were confined to the study of chemotherapy of tuberculosis based on the Veterans Administration-Army-Navy Cooperative Studies. The last one appeared in July, 1955, in which he announced dates in February, 1956, for holding the 15th conference.

Some persons have considered Dr. Walker's leadership and papers in the Veterans Administration studies of anti-tuberculosis drugs as his greatest work, while others place the Technical Bulletin in this category. Most certainly, a combination of the two placed him at the summit of the world's activities and contributions in medical writing and in the chemotherapy of tuberculosis.

Those who were fortunate enough to be invited to make a formal presentation before one or more of the Veterans Administration-Army-Navy yearly conferences during the past decade caught at least a glimpse of Dr. Walker's greatness. His invitations were so graciously expressed, his praise and encouragement after papers were read inspired workers to continue their labors and give to the world everything they had or could produce in chemotherapy.

On the night of December 12, 1955, Dr. Walker retired with a vision of accomplishments ahead which probably no other living person had. Although he died while he slept that night, he left a rich heritage. In the entire history of treatment of tuberculosis, no one before him had accomplished so much. Through his organization and inspiration he had kindled so many fires which will keep burning in the lives of others to insure the realization of his visions.

J. Arthur Myers, M.D.

HOTEL RESERVATION FORM

22nd ANNUAL MEETING
AMERICAN COLLEGE OF CHEST PHYSICIANS
Hotel Sherman, Chicago, Illinois, June 7-10, 1956

The 105th Annual Meeting of the American Medical Association will immediately follow the College meeting in Chicago, June 11 through 15, 1956.

Please send this form to the Hotel Sherman at once—requests for reservations will be accepted in the order received.

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Comments.....

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CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

22nd Annual Meeting, American College of Chest Physicians
Hotel Sherman, Chicago, Illinois, June 7-10, 1956

Fourth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Cologne, Germany, August 19-23, 1956

CHAPTER MEETINGS

New York Chapter, New York City, May 10, 1956

Florida Chapter, Miami Beach, May 13, 1956

Georgia Chapter, Atlanta, May 13-14, 1956

New Jersey Chapter, Atlantic City, May 16, 1956

Illinois Chapter, Chicago, May 17, 1956

Minnesota Chapter, Rochester, May 21, 1956

MEDICAL SERVICE BUREAU
POSITIONS AVAILABLE

Tuberculosis physicians wanted to staff new 200-bed, air-conditioned sanatorium, opening July 1, 1956. Adjacent Medical College of Virginia and its hospital; complete facilities available for chest surgery, surgical and other consultation; out-patient clinics; occupational therapy; rehabilitation; opportunities for teaching and research; eligibility for licensure in Virginia required; all positions covered by social security, state retirement, vacation and sick leave.

Medical Director: position open now. Salary range $12,000 to $13,128; five or more years' clinical experience in tuberculosis, four of which served in approved sanatorium and one year in a senior grade; one or more additional years' satisfactory experience may be substituted for sanatorium service; Board certification, internal medicine, desirable.

Physician B (3): Salary range, $9,600 to $11,472; two years' experience in approved tuberculosis sanatorium or two years in clinic or office practice under supervision of competent chest specialist; two years general practice may be substituted for one year sanatorium or non-sanatorium specialized chest disease experience.

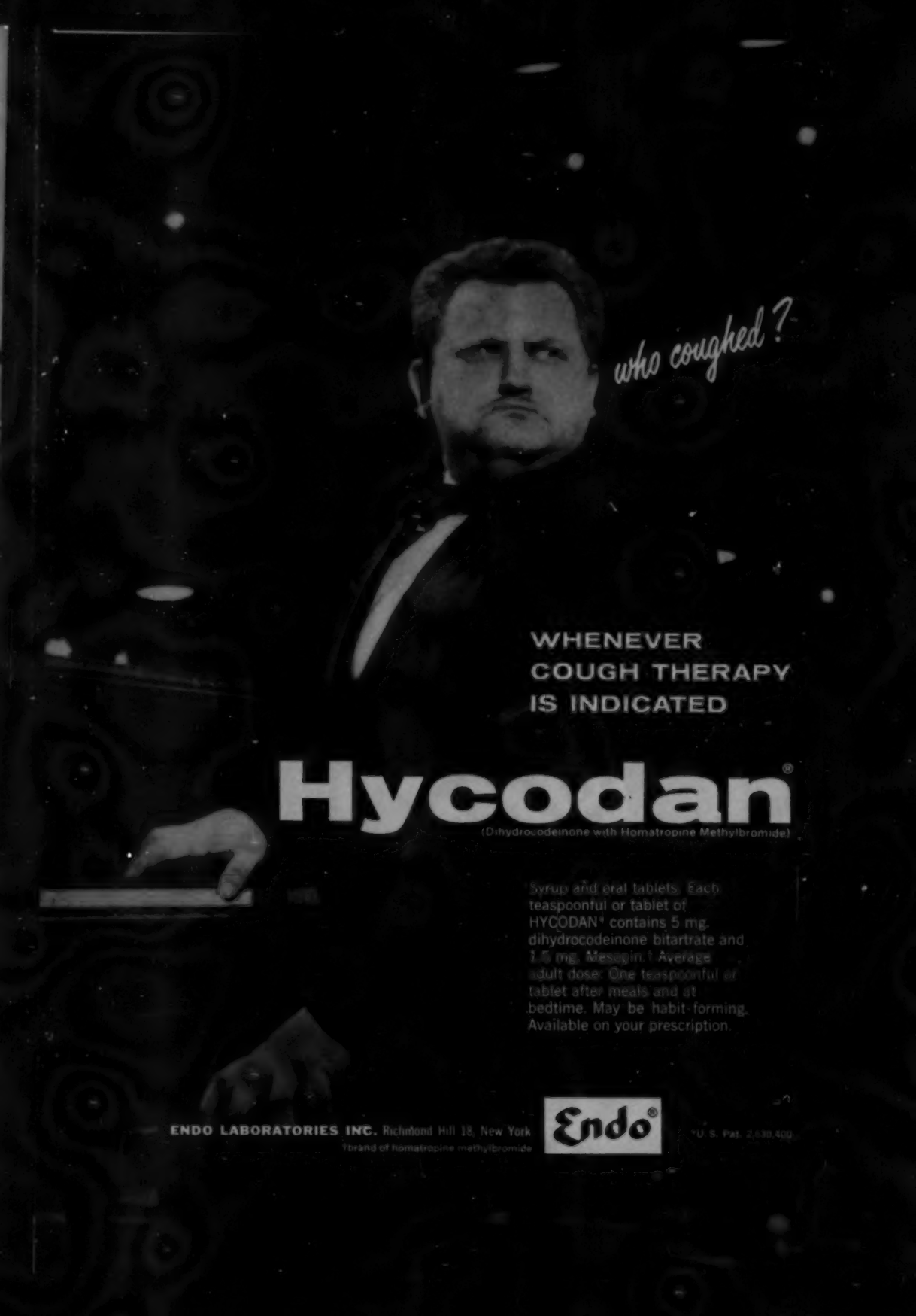
Physician A (1): Salary range $8,400 to $9,168.

Apply to Mack I. Shanholtz, M.D., State Health Commissioner, Department of Health, Richmond 19, Virginia.

Winfield Hospital has openings for physicians who are experienced in tuberculosis programs. Please contact Dr. David B. Radner, Medical Director, Winfield, Illinois.

Assistant medical director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, 100-bed county tuberculosis hospital with active medical, surgical, out-patient and investigative programs. Salary determined by experience. Furnished home and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address: E. V. Bridge, M.D., Superintendent.

Physician wanted for institutional appointment, preferably with experience in the diagnosis and treatment of tuberculosis, although not essential. Must be eligible for or have Oregon license. Higher salary if experienced in chest surgery. Starting salary $7,600 with complete maintenance. Please address all inquiries to Box 287A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.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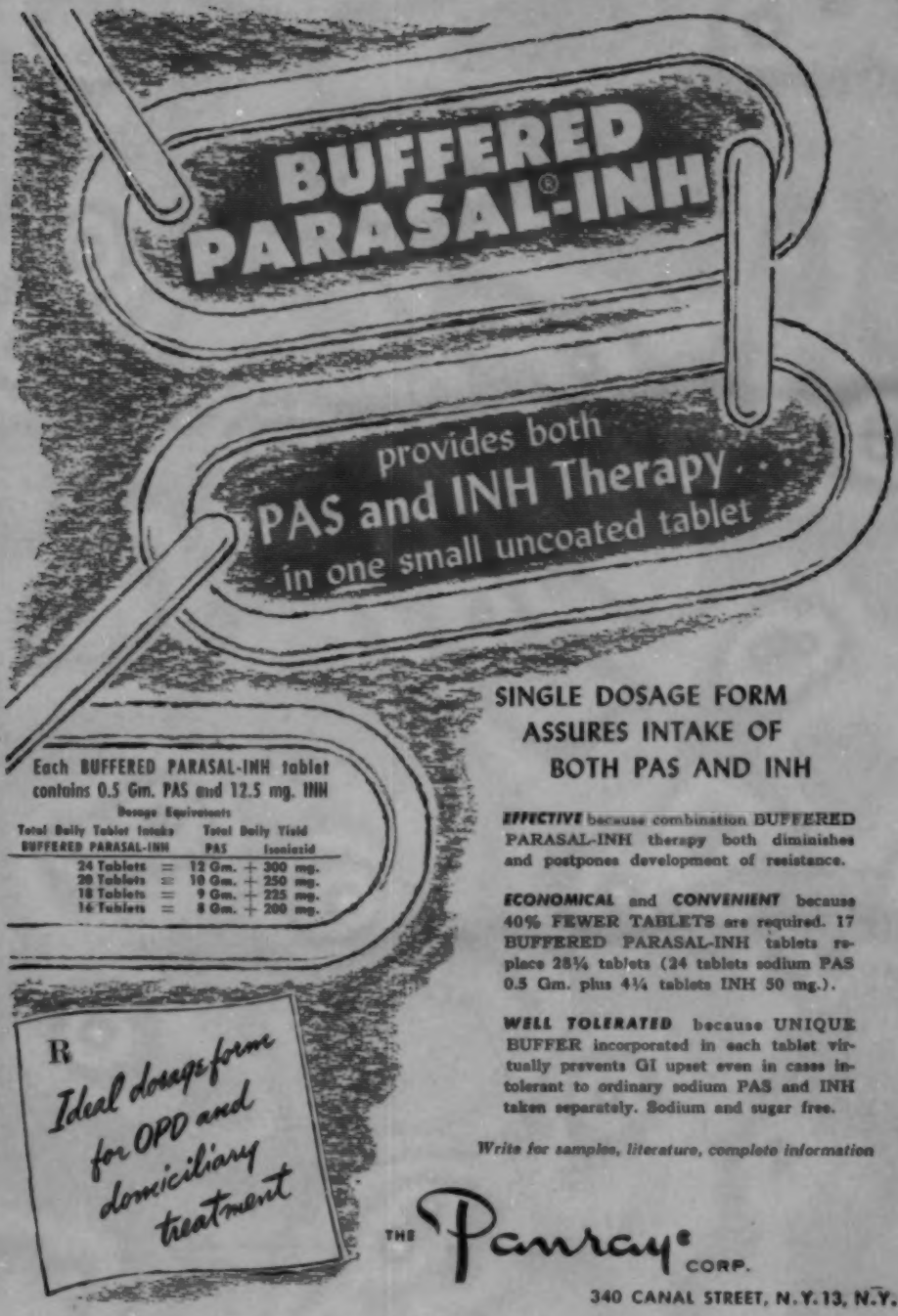

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